UNITED STATES OF AMERICA

+ + + + +

DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

+ + + + +

NEUROLOGICAL DEVICES PANEL OF THE

MEDICAL DEVICES ADVISORY COMMITTEE

+ + + + +

TWELFTH MEETING

+ + + + +

FRIDAY,

SEPTEMBER 17, 1999

+ + + + +

The meeting was held in Room 20B of the Center for Devices and Radiological Health, 9200 Corporate Boulevard, Rockville, Maryland at 7:45 a.m., Dr. Alexa I. Canady, Panel Chairperson, presiding.

PRESENT:

ALEXA I. CANADY, M.D., Panel Chairperson
EVERTON A. EDMONDSON, M.D.
CONSTANTINE A GATSONIS, Ph.D.
GILBERT R. GONZALES, M.D.
ROBERT W. HURST, M.D.
ANDREW KU, M.D.
SALLY L. MAHER, Esq.
RICHARD D. PENN, M.D.
PEDRO PICCARDO, M.D.
CEDRIC F. WALKER, Ph.D., P.E.
ANNE W. WOJNER, M.S.N.
JANET L. SCUDIERO, M.S., Executive Secretary

PRESENTERS:

STEPHEN RHODES
THEODORE MALININ, M.D.
P.J. PARDO
RUTH SOLOMON, M.D.
KEVIN DALY
KEITH FOX
LISA WEBB
KRISTEN A BOWSHER, Ph.D.
DREW JOHNSON
TRACY CAMERON
JOHN ERIKSON
BOB KLEPINSKI
RICHARD NORTH, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(7:58 a.m.)

CHAIRPERSON CANADY: If the room can get quiet we're going to begin some of the housekeeping now so that we can start with Dr. Malinin right at 8 o'clock.

Ms. Scudiero is going to read off the disclaimers.

MS. SCUDIERO: Okay. Good morning, again. I have the conflict of interest statements to read for today and also for the temporary voting statements appointments.

The conflict of interest statement for today's meeting. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibits special government employees from participating in matters that could affect their or their employers' financial interests. However, the Agency has determined that the participation of

certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government. Waivers have been granted for Drs. Constantine Gatsonis and Richard Fessler and Dr. Fessler is unable to attend, for their interest in the firms that could potentially be affected by the Panel's deliberations. The waivers allow these individuals to participate fully in today's discussion.

A waiver has also been granted for Dr. Richard Penn for his interest in firms that could potentially be affected by the Panel's deliberations. The waiver allows him to participate in the guidance document discussion for artificial embolization devices. Copies of these waivers may be obtained from the Agency's Freedom of Information Act Office, Room 12A-15 of the Parklawn Building.

We would also like to note for the record that the Agency took into consideration certain matters regarding Drs. Gatsonis, Fessler and Cedric Walker. These individuals reported past or current interest in firms at issue, but in matters not related to the topics for today's

discussion. Therefore, the Agency has determined that they may participate fully in the deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment on.

The next statement is an appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27, 1990, and amended August 18, 1999, I appoint the following as voting members of the Neurological Devices Panel for the duration of this meeting on September 16 and 17: Constantine A. Gatsonis, Ph.D. on September 17th; Robert W. Hurst, M.D., on September 16th and 17th; Richard D. Penn, M.D., on September 16th and on the morning of September 17th for the

discussion of the draft guidance document for neurological embolization devices. For the record, these people are special government employees and are consultants to this Panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This is signed by Dr. David W. Feigal, Jr., Director of Center for Devices and Radiological Health on September 9, 1999.

One more statement. Pursuant to the authority granted under the Medical Devices Committee charter of the Center for Devices of Radiological Health, dated on October 27, 1990 and amended August 18, 1999, I appoint Dr. Pedro Piccardo, M.D., as a voting member of the Neurological Devices Panel for this meeting on September 16th and 17th. For the record, Dr. Piccardo is a voting member of the Transmissible Spongiform Encephalopathies Advisory Committee and the Center for Biologics Evaluation and Research. He has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. This is signed by Linda A. Suydam, Doctor of Public Administration,

Senior Associate Commissioner on September 15, 1999.

CHAIRPERSON CANADY: I'm Alexa Canady, Chairman of the Neurological Devices Panel and I'm a Pediatric Neurosurgeon at Children's Hospital of Michigan in Detroit. Yesterday, we made recommendations on the draft guidance document for dura substitute and started on the classification of human dura when the lights went out. Today, we'll finish on that classification and proceed with making recommendations on the schedule topics for today. The draft guidance document for neurological embolization devices and the reclassification petition for totally implanted spinal cord stimulation.

I would like to note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

Before we begin the meeting, I would like the Panel Members again to introduce themselves, starting with Dr. Penn.

DR. PENN: Richard Penn. I'm a neurosurgeon from Chicago.

DR. GONZALES: Gilbert Gonzales. I'm a neuroncologist from Memorial Sloan Kettering Cancer

Center in New York City.

DR. PICCARDO: Pedro Piccardo, Indiana University, Neuropathology.

DR. WITTEN: Celia Witten, FDA Division Director, DCRD.

MS. MAHER: Sally Maher, Industry Representative, Wesleyan Biomedical.

DR. WALKER: Cedric Walker, Professor of Biomedical Engineering, Tulane University.

DR. KU: Andrew Ku, Allegheny General Hospital. I'm a neurointerventional neuroradiologist.

MS. WOJNER: Anne Wojner, Assistant Professor, Clinical Nursing, University of Texas at Houston and Clinical Nurse Specialist, Nurse Researcher, Division of Stroke Neurology, UT Med School.

DR. EDMONDSON: Everton Edmondson. I'm a neurologist, neuroncologist, pain management specialist from Houston.

DR. HURST: Robert Hurst. I'm an interventional neuroradiologist, University of Pennsylvania.

CHAIRPERSON CANADY: Thank you very much. We'd like to return to our open session from

yesterday with one scheduled speaker, Dr. Thomas Malinin from the University of Miami. Theodore Malinin. I've screwed it up both days.

DR. MALININ: Well, that's close enough. I've given you some historical background yesterday just before the lights went out on dura mater allografts. I do apologize to the Panel Members for not bringing the visual aids for this presentation, but I did not know I was going to be attending this meeting until the beginning of this week.

As we have mentioned, I have been involved in preparation of dura mater allografts for some 30 years from the day of their inception at the Naval Medical Center. We have continued to do so. Clinically, I'm told by my neurosurgical colleagues that these have been effective materials for substitution of vacuole meningeal defects.

Dura mater is a very unique and a peculiar structure. We have described the fibroid orientation in this material, both by light scattering and by polarized microscopy. We've published these results in The Journal of Anatomy last year. The dura mater has been tested biomechanically and the results of these have also

been published in Biomaterials Journal. We find it difficult to find any other structure in the body with which we compared dura mater which is comparable.

Dura mater when it is not subjected to treatments, but is simply freeze dried and sterilized with ethylene oxide as we do it, is biomechanically compatible to frozen and untreated dura. If we subject it additional treatments it becomes stiff and the stiffness, although probably does not impede transplantation of small patches of dura which are rectangular, does make the large grafts very, very non-pliable and difficult to implant.

The safety measures we're obviously concerned with. The FDA has instituted a general guidance for selection of donors for all tissues for transplantation. We follow these religiously. In fact, we were one of the tissue banks which was responsible for instituting these guidelines or advocating it. All of the donors of dura mater that we process in our institution are subjected to a complete autopsy, always have been and although this is not an FDA requirement, in the processing of dura maters each donor is treated separately and

there is absolutely no commingling between individual donors when these duras are being processed.

Each dura mater is cultured individually before it is packaged to eliminate the possibility of transmission of infection. A great deal has been said and paid attention to with regard to Jakob-Creutzfeldt Disease, the possibility of transmission. This is really the least of our concerns. Our large concerns is a possibility of transmission of HIV and hepatitis. To the best of my knowledge there has not been a single case of Jakob-Creutzfeldt Disease being transmitted with dura mater transplants that have been processed in this country and certainly not in the 50,000 of ones that we have processed.

To eliminate the possibility of transmission of other diseases, donors are being scrupulously screened by all available methodology. Again, we examine lymph nodes for possibility of undetectable HIV infection. We do antigen tests. We do all of the serological available tests. And we also do the same for all of the types of hepatitis that have been presented with us.

The doses of irradiation that have been

used in the past, we now know are not adequate certainly for an activation of HIV. Therefore, the selection of the donors and screening of the donors still remains the best method of preventing the possibility of disease transmission with any type of a graft, including dura mater.

The material on dura mater has been presented to this Panel in a meeting of 1990. I see that the Members of the Panel have now changed, but I presented very much the same material except now we have more updated information on it. At that time the Panel recommended that dura mater allografts be classified as Class II devices. I think it is a very reasonable classification and I would certainly endorse such at classification.

There have been a number of questions raised with regard to this graft. This graft has been singled out as being regulated by -- as a device along with the heart valves. No other type of human tissue has been subjected to this regulation and whether this will remain so or whether this will be amalgamated in the general tissue transplant program obviously is something that FDA is going to determine as time goes on.

But in summary, in my experience dura

mater grafts have been very useful to neurosurgeons with which we deal, certainly in our institution. They continually urge us to make them available for their patients. We have not encountered any major problems and we do track the recipients and certainly in our own institution which is a sort of an internal safety program and quality assurance program. We have been implanting, in our hospital, these grafts since 1970. As I mentioned, we have distributed throughout the country in this last 30 years some 50,000 such grafts without any other problems that have been recorded. We certainly have not transmitted infections and we were able by careful selection and studying of the donor prevent the possibility of transmission of diseases which could be transmitted with any type of the tissue being transplanted.

If there are any specific questions that the Members of the Panels wish to ask me, I would be happy to answer such.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: Yes, you alluded to the sodium hydroxide preparation being bad for the handling characteristics of the dura. Do you want to speak more about that because that's one of the

major issues in the guidance that we'll be discussing.

DR. MALININ: Well, sodium hydroxide does make dura mater stiff. And it's apparently quite all right if the grafts are small, but if they're large, they're very, very difficult to manipulate. The usefulness of sodium hydroxide in activating prion disease has not been fully established. There have been a number of other possibilities including Dakin solution and the hydrochlorides and the life that could be treated.

The ethylene oxide has not been subjected to a thorough investigation in the study. In fact, I find it very difficult to find a laboratory which would test it for as definitively because it has to be done with a scrapies virus model and the results would take approximately a year to two years to be known. We are very much interested in pursuing this study and I hope that we will find a collaborating laboratory which will perform them for us.

The second problem with sodium hydroxide, obviously, with a large graft, the larger the graft the more the absorption of

material and more possibility of leaking out. No matter how much you wash it, there is a residual which is going to be bound to the tissue and might precipitate arachnoiditis in various undesirable reactions, so we're very, very concerned about that.

Ethylene oxide sterilization, likewise produces residuals, particularly chlorohydrin and ethylene chlorohydrin and propylene oxide which have been defined in the FDA guidelines in which we are able to remove to nondetectable levels by chromatography.

So I don't have a very positive feeling about sodium hydroxide sterilization as far as the dura mater is concerned because of its biomechanical undesirable side effects and the problem would be are we willing to trade these for the alleged delamination of the risk that such treatment would afford. I think there probably will be other chemicals. Yes, they're all specified in the guidelines that would be used.

CHAIRPERSON CANADY: Other questions? Dr. Piccardo?

DR. PICCARDO: You mentioned autopsy studies on the donors. What about specifically the

neuropathologic studies that you're doing?

DR. MALININ: Well, it is -- in pathology circles it is a very touchy question. The majority of the donors which are -- from which dura maters are obtained are falling without medical examiners' jurisdiction. The medical examiners would allow the brain to be examined by neuropathologists or asked for neuropathological help if there is an indication for them to do so, but none of them are willing to turn their entire brain over for somebody else to examine when they are responsible for an autopsy. And this is true in general autopsy services. So somewhere, somehow we need to reach an agreement, whether we will submit histological sections for a neuropathologist to look and to close, but the examination of the entire brain on every donor practically would be impossible in medical examiner settings.

CHAIRPERSON CANADY: Other questions for Dr. Malinin?

Thank you very much, Dr. Malinin.

Is there anyone else who would like to make public comment? Not so, then we'll close the Open Session for the public and we'll go to the Open Session for the Panel. Our primary reviewer

in this case is Dr. Piccardo and he has a presentation for us.

DR. PICCARDO: Can we dim the lights a little bit, please? Not so much. Okay.

First of all, thank you for the opportunity to present this data. And my mission here is to review the complexity of these diseases. To that matter, my idea was to present some general concepts, to review the pathology of the frequently seen pathology, but also of the not frequently seen pathology and I think this is critical when we talk about surveillance and then some basic molecular data that we've been gathering.

I guess the first message is that this is secondary genus group of disorders and so the take home message is heterogeneity. We called them, for example, transmissible, spongiform and pathology of prion diseases. As you will see, not all of them have been shown to be transmissible, for example, and not all of them have spongiform changes. This is important because in pathologies, if we only looked for spongiform changes, then some of the cases will be misdiagnosed.

In humans, we have a large list of

diseases in which we have the origin idiopathic for sporadic Creutzfeldt-Jakob Disease which is that disease which we all know well and there are also acquired forms of the disease in which we have kuru that was due to the ritual of cannibalism. Iatrogenics CJV that we are already aware in this Panel and now we have the surprise of the new variant CJV. We have to the best of my knowledge up to the date 46 cases, 45 in England in the UK and one in France. And the new variant has been linked to the epidemic of bovine spongiform encephalopathy.

And then we have inherited forms of prion diseases in which we will have German Straüssler Scheinker. We will have familial Creutzfeldt-Jakob and Fatal Familial Insomnia.

Once again, heterogeneity, for example, in Creutzfeldt-Jakob Disease which is the disease that we know so well, the presenting clinical sign is dementia. The mean age of adult onset is in the late sixties, the pathology, the dominant pathology of spongiform changes.

Let's take, for example, new variant Creutzfeldt-Jakob Disease. The mean age of adult onset is in the late 20s. The duration is longer,

where the duration is sporadic for Creutzfeldt-Jakob Disease, usually six months, here we are over 14 months.

While the electroencephalogram here usually is or many times is diagnostical -- or is helpful for the diagnosis, very helpful for prognosis, it is not in the new variant. The pathology is also different. While in sporadic Creutzfeldt-Jakob Disease we do not have the position of prion protein amyloid. In the new variant, we have the position of prion protein amyloid as one of the hallmarks of the disease.

Then when we come to Fatal Familial Insomnia, we'll see that these diseases do not have spongiform changes and the pathology is mostly thalamic. So once again, if a pathologist is looking for spongiform changes for the diagnosis, definitely will misdiagnose, for example, Fatal Familial Insomnia.

Many cases of German Straüssler Scheinker Disease do not have spongiform changes, although they have a lower familial position. The differential diagnosis in these diseases include Alzheimer's disease and other diseases as we'll see later.

Therefore, the message that I want to convey to you is that it's important not only to look for what we know, but also to look for what the rare forms and also to be very careful in the differential diagnosis with other neurologic diseases because some of these spongiform encephalopathy or prion diseases will mimic other disorders such as Alzheimer's Disease.

We do have other -- this is also seen in animals and we have scrapie in sheet and goat, chronic wasting disease in deer and elk, and of course, we have the well known bovine spongiform encephalopathy.

So I talked already about the heterogeneity or I touched upon the heterogeneity, so what seems to be common in all these disorders, is the accumulation of the prion protein which is a protein that we all do have here and that hopefully we all have the normal protein, but sometimes things go wrong and our protein is misfolded and then we'll get the disease.

From a molecular point of view, the protein is encoded by a gene that is present in chromosome 20 and from a structural point of view, we can divide this protein into two parts. This is

the amino terminal portion and this is the carboxyl terminal portion and when we had an end terminal that is pretty wobbly, we have a middle part and a C-terminal part that is fairly structured.

What we do have is that while in the normal protein there is a prevalent alpha helix configuration. When the protein folds in an abnormal way we will have an increase of PrP structures in this area.

The normal protein tends to be soluble and usually is degraded by proteases, like proteinase K. The abnormal protein is insoluble and is resistant to proteases, so we can use those parameters to make, to help in the diagnosis of the disease from a biochemical point of view.

A prevailing hypothesis states that we do have -- these would be the normal protein which is PrPc for cellular. This would be the normal protein that we all have and if that protein encounters an abnormal protein, let's say this black icon here, we will have heterodimer. And the abnormal protein will force the normal protein to fold abnormally and this will make an abnormal heterodimer. And so on and so forth, so this is a prevailing hypotheses to try to explain why we

develop these diseases.

Why do we have the abnormal protein here? Well, it could be that we are injected with the abnormal protein like in cases of iatrogenic. In other cases, we don't know why some of our molecules might go wrong, fold abnormally. And in other cases there are genetic reasons for these. We have mutations and therefore that mutation makes that protein prone to fold abnormally.

This is work that was done at NIH and Dr. Gibb's and Gajdusek's work many years ago when I was at NIH. And the finding here is that when we purify the protein what we see in cases of animals infected with these diseases we purify the protein and we end up having these fibroids. These fibroids have amyloid properties from a pictorial and physical point of view and we did also immunoelectromiscropy, as you see here, these black dots represent gold that is attached to an antibody that will recognize the prion protein. So these amyloid fibers are composed mostly of prion protein.

What happens is when we purify this material, if we put it on the electron microscope, we will see these which I'm showing you now. And

if we inject these into another animal's brain, the other animal will develop the disease.

An interesting finding during those studies was that these abnormal fibers are also present in non-neuronal tissues. For example, here we can see -- we were able to extract these amyloid fibers from a spleen.

So let's go into the biochemistry a little bit. Here we have controls. In this case, I'll use Alzheimer's Disease. When we run a Western Blot what we see here is that the prion protein that will be completely degraded by proteases so this is -- although this corresponds to a patient with Alzheimer's Disease, this definitely corresponds to a case of a nonprion disease.

So our cells, we should fall into this category. We have the prion protein, but if we treat it with proteases, we degrade it completely.

Now what happens with a patient with Creutzfeldt-Jakob Disease? This patient will also have the prion protein, as you see here, but if we treat it with proteases, there will be a procedural core that is protease resistant and this is very helpful in the diagnosis.

Now if we want to make things even simpler, we can use the glycerin basis, so we'll removed all the sugars and these three isoforms that represent different forms of the protein with different amount of sugars will fall into one isoform of approximately in this case 21 kilodaltons.

What about the pathology? Yes?

DR. EDMONDSON: What's the last column, IK?

DR. PICCARDO: I tried to avoid that for the time being, but you are asking me, so I will answer. This corresponds to a form of German Straüssler Disease and I will talk to this, I will touch upon this issue later.

What I'm trying to show here is that the heterogeneity is also present at the biochemical point of view and while most of the people can recognize this very well, the protein without treatment and the protein after treatment, when we come across diseases with different phenotypes we might find different abnormal isoforms of the protein and I think that is important for the diagnosis. I will touch upon that later. There is a section on German Straüssler.

Regarding the pathology, what we see here is what the pathologists know so well and this is the most frequent form of the disease. This corresponds to a case of Creutzfeldt-Jakob Disease. Here, we have the meninges. This is the surface. Here, we have the white matter and here we have the cortex. And as you can see, this cortex is full of these holes. This is a spongiform encephalopathy. This corresponded to a case of Creutzfeldt-Jakob Disease. This is very easy to diagnose.

In the same case when we perform immunostaining to detect glias, these are astrocytes and you can see there is an extensive gliosis. So spongiform changes and gliosis are the hallmarks for Creutzfeldt-Jakob Disease.

Now when we take material coming from those patients and we inject, for example, in this case a mouse, in this case this corresponds to a control. This would be a mouse, a control mouse in which we see the hippocampus the white matter and the cortex.

This corresponds to a mouse that was injected with material coming from Creutzfeldt-Jakob Disease and after a hundred days this animal

developed a spongiform encephalopathy with gliosis. As you see here, we see the holes representing the spongiform changes in the cortex and in the hippocampus and we also see the gliosis. These brown spider shaped cells are reactive glia. So this is simple to diagnose and well, these are the most frequently observed cases.

So to wrap up this part is the neuropathology of the transmissible spongiform encephalopathy of prion diseases in most cases we will see spongiform changes. We will see neuronal loss and we will see gliosis. This is what I showed you already.

Now I also -- I will show you that there is also accumulation of prion protein in the Central Nervous System, that there is no conventional host inflammatory response and in some cases, there are amyloid deposits. What I pointed out already and I want to point out again is that in rare forms of this disease sometimes we do not see spongiform changes and we see a lot of amyloid depositions. Sometimes we see neurofibrillary tangles as we see in Alzheimer's Disease. Sometimes we even see Louis bodies as we see in Parkinson's Disease.

Therefore, the differential diagnosis is important and for the surveillance it's important to consider that there are very unusual forms of this disease from a pathologic point of view.

So now I will touch upon genetic forms of these diseases and once again this is the prion protein. This is the amino terminus, this is the carboxyl terminus and there are -- this slide is always outdated because we keep on finding more and more mutations.

For example, last year, we found mutation 202 and 212. Now what I point out is that there are a number of missense mutations that are found in the gene and we keep on finding more and more as I said already. The important thing is that some of these mutations go with a certain phenotype that corresponds to that Creutzfeldt-Jakob Disease, while other mutations go along with a phenotype, that falls more into the German Straüssler Scheinker Disease phenotype, meaning usually clinically there is a longer clinical course and pathologically there is amyloid accumulation and in many forms of German Straüssler Disease we do not see spongiform changes.

The other part of the thing that is

important from a molecular point of view is to recognize that these proteins are polymorphic 129. So we all have the prion protein here. Some of us will be homozygote. Some of us will be homozygote in the thiamine. And some of us here will be heterozygote in the thiamine invading. This seems to be important because if we are homozygotes it seems that we will develop the disease earlier and the clinical course will be shorter.

So once again to wrap this up, we have the traditional forms or the most frequently forms of this disease. This corresponds to Creutzfeldt-Jakob Disease. This corresponds to cortex, this to basal ganglia and this to cerebellum. And what we see here are spongiform changes. In the cortex and the basal ganglia and the cerebellum we see accumulation of prion protein and we see gliosis.

Now, here I will touch upon rare forms of this disease and here, we have two examples. These are two genetic forms. This is German Straüssler. The upper part corresponds to a family that had a mutation at Column 102. This corresponds to two different members of this family, this kindred. All of them had amyloid blocks as seen with thioflavin. All of them had

prion protein accumulation. Some of the members, some of the patients from this family had spongiform changes. Others did not. So there is heterogeneity even in members of the same family.

Now the lower part of this is of particular interest to us or to me, at least, because this family was diagnosed as Alzheimer's Disease. Let's concentrate on Panel E. What we see here is thioflavin. This is a technique for amyloid. What we see is that this corresponds to amyloid blocks and these tiny little things there, the rods, correspond to neurofibrillary tangles.

So any pathologist with that slide will tend to think about -- seriously, about Alzheimer's disease. This is a patient with dementia. This is a patient that the clinician thought corresponds to a family of Alzheimer's Disease and the pathologic findings were similar to those seen in Alzheimer's Disease.

But what happened? We perform immunohistochemistry for prion protein and there is a lot of prion protein accumulation in this case. This family was originally studied by Dr. Getting at Indiana, and this corresponds to the Indiana kindred.

Also, immunohistochemistry in this case shows that on top of having prion protein accumulations, severe prion protein accumulation, this is immunohistochemistry for tau, the protein that makes the neurofibrillary tangles characteristic of Alzheimer's Disease. So what we see in this family is that there is a lot of prion protein accumulation, but there is also a lot of tau pathology which is the pathology that we see in Alzheimer's Disease.

So this is -- well, this is sequelae sequencing, this is the direct sequencing of the PRBG and members if this family and we see the mutation at Column 198.

So we performed biochemistry on these patients and I ask you to please remember the classical pattern in Western Blot of prion protein in Creutzfeldt-Jakob Disease. What we see here is a very, very different pattern. We see in different areas of the brain of these patients and we study many, many patients from this family.

Actually, we performed biochemistry on seven patients from this family and in all of them we see an identical pattern. We see their accumulation of a low molecular weight band and we

also see an upper component, meaning prion -- protein is a resistant prion protein, different from those seen in Creutzfeldt-Jakob Disease.

So this was of particular interest to us because it's telling us that we, when we attempt to analyze from a biochemical point of view of prion diseases, we have to look for unusual patterns of Western Blot.

This line you can see here we can compare. In there it corresponds to a case of Creutzfeldt-Jakob Disease. This is following proteinase K treatment. We see the three isoforms. The isoform of prion protein with no sugars, with one sugar and with two sugars and this is characteristic of Creutzfeldt-Jakob Disease.

Look at the pattern in this family with mutation at Column 198. See how different it is. In order to make sure that we are dealing with something very specific, we perform a sequence, we purify this band and we perform the sequence and we saw that this corresponds to prion protein. To the middle part of the prion protein

So now I will use as an example, another family with a mutation at Column 102. Basically, this light is to remind me that now I'm going to

talk about mutation 102, but I also want to point out that what we did was to make synthetic peptides to the different parts of the prion protein and we erase antibodies against older regions with the attempt of analyzing bio-immunohistochemistry and biochemically the degradation of the prion protein in different forms of prion diseases.

So this corresponds to a patient, a kindred mutation 102 and as you can see here, there are amyloid blocks. For example, here. This is an amyloid block. This is a hemotoxin. What you do not see are spongiform changes.

This is another member from the same family and you see amyloid blocks, but you see spongiform changes. Once again, pointing to the heterogeneity of these disorders, even in members of the same family. All of them have accumulation of prion protein in the brain.

We performed immunohistochemistry. I'm not going to show you all the data. And what we found is that the amyloid in this family was immunolabeled by antibodies to the mid region of the prion protein, but was not labeled using antibodies to the amino or to the carboxyl terminal region of this protein.

So therefore it is important to perform immunohistochemistry to make the diagnosis and also it is important to use the right antibody.

We performed biochemical studies and I'm not going to go into any detail on this slide, but I want to point out two things. Once again, A and B corresponds to Creutzfeldt-Jakob Disease. As you see, this is the pattern of PRP without any proteinase treatment and this is the pattern of the proteinase K resistant prion protein after protease treatment. You see this is the classical pattern and we see the shift down because the amino terminal part is cleaved.

Now what we see here from C to J are members of -- I mean people with German Straüssler Disease with mutation at Column 102 and while some people with German Straüssler Disease with Mutation 102 have a pattern that is very, very similar to that seen in Creutzfeldt-Jakob Disease, there are others that do not have that pattern at all.

For example, J. You see we do not see this upper component as we see in Creutzfeldt-Jakob Disease. This is important because we have to know in order to see the proteinase K resistant prion protein in J in this patient, we have to load more

and we have to expose this film more. So if you perform a conventional Western and you are not very, very careful, you will miss it. For example, F, you see? There is almost nothing. The insert corresponds to a longer exposure of this field on this region.

So as you see while Creutzfeldt-Jakob Disease, this patient with Creutzfeldt-Jakob Disease did not have a low molecular weight proteinase K resistant prion protein band. All the German Straüssler Scheinker patients did have it. Some patients with German Straüssler Scheinker Disease had very, very small amounts of proteinase K resistant prion protein. So I guess what I'm saying is once again for the surveillance, we have to be careful when we perform Western Blot and we have to look for some cases that will tend to accumulate low amount of prion protein and we have to look for unusual patterns.

This is another example. This is a mutation that we found last year at Column 212. And once again we do not see spongiform changes here. But we see prion protein accumulation. And the pattern corresponds to a pattern that is similar, but not identical to that seen in the

Indiana Mutation 198. That is very different again from that seen in Creutzfeldt-Jakob Disease. And once again, this patient with Mutation 212 accumulated a low amount of prion protein in the brain.

This is a very busy slide. All I want to point out to you is that we performed analysis in many, many cases with different mutations with German Straüssler Scheinker Disease with different mutations. What I want to point out to you was the clinical diagnosis in some of these cases.

For example, Patient 1 was diagnosed clinically as polybroponto cerebellar atrophy. Patient 2 as German Straüssler. Patient 3 as cerebelloponto cerebellar atrophy. Some of these patients were diagnosed with Creutzfeldt-Jakob Disease. Some had the diagnosis of dementia. Some had the diagnosis of cerebral degeneration. In patients with Mutation 117, this patient was diagnosed with Parkinson's Disease. With patient with Mutation 202 was diagnosed with Alzheimer's Disease. So as you see, this is not straight forward.

And this is the Western Blot, a summary of the Western Blot performed on all those

patients. What you see is that once again the patients with German Straüssler Scheinker Disease have a pattern that is different from that classically seen in Creutzfeldt-Jakob Disease for the presence of a low molecular weight band and for the presence of other bands that sometimes are not very abundant. So we have to be careful and look for low band -- once again, usual patterns in Western Blot.

This is a case that we had a chance to study a few years ago and what you see here is in Panel A is this is thioflavin. This patient came from Japan, well, actually the brain was sent from Japan. The patient was never in the U.S. The clinical diagnosis was Alzheimer's Disease and what we see here is with thioflavin a lot of neurofibrillary tangles. So this corresponds to the diagnosis of Alzheimer's Disease. You expect to see a lot of neurofibrillary tangles in a patient with Alzheimer's Disease. We performed immunohistochemistry to the tau protein present in the neurofibrillary tangles using many, many different antibodies. This is a panel of antibodies against these foreign regions of the tau molecule and as you see, these are similar to what

we will see in Alzheimer's Disease.

Now we also perform immunohistochemistry for prion protein and what we see here is that this patient accumulated a lot of prion protein, but the accumulation of prion protein in this case was around the vessels. So this was a prion protein amyloid angiopathy.

Usually in prion diseases the amyloid accumulates in the parenchyma. Here, we see the accumulation of prion protein accumulates mostly around the blood vessels, so although this is only one patient, this is very, very rare. It calls our attention that every time we come across a patient with dementia that has amyloid angiopathy we better perform immunohistochemistry to prion protein. So this was published in 1996 in PMAS and so this is sort of a new entity, a new phenotype which is a prion protein cerebral amyloid angiopathy.

This is electromicroscopy. This is the lumen of the vessel. This is the wall of the vessel and here you can see the amyloid, the prion protein amyloid block in the wall of the vessel of this patient.

And this is immunoelectromicroscopy and this corresponds to a neuron and these are the

neurofibrillary tangles that the patient has that are identical to those seen in Alzheimer's Disease. So to wrap up this entity, this patient was diagnosed clinically as Alzheimer's Disease, had neurofibrillary pathology identical to that seen in Alzheimer's Disease. However, had a prion protein similar to amyloid angiopathy.

Let me see, yes, on top of all of this, we have the new variant Creutzfeldt-Jakob Disease and this slide this was kindly given to us by Dr. Peter Lantos and James Ironside in the U.K. and now we go back to a spongiform encephalopathy. This corresponds to the new variant that has been described in England by Bob Will and James Ironside and what we see here is amyloid and around the amyloid we see what they describe as a flooded placque because there are a lot of fibroids around this amyloid and they claim that this is very classical for this disease.

There are a lot of spongiform changes, however, the spongiform changes are not prevalent in the basal ganglia more than in the cortex and there is a lot of prion protein accumulation as we see here. This is immunohistochemistry for prion protein in the cerebellum and you see that these

patients die with a humongous demand of prion protein accumulation in the CNS.

Once again, coming back to the reagent, it is very critical to use the proper antibody. In our attempt to try to understand better if there was any correlation between the bovine spongiform encephalopathy and the human diseases we developed an antibody that is raised against a conserved region of the prion protein in order to be able to perform immunohistochemistry on Western blot analysis in animals of different species that come down with the disease and also to perform immunohistochemistry.

The idea was to see if we could find a pattern of prion protein that would be singular in the animals with the disease and in the new variant. This is work that was finally was done by John Collins in England at St. Mary's in England and he published that paper showing that in the new variant Creutzfeldt-Jakob Disease there is a pattern that is different from that he claims a pattern that is different from that conventionally seen in Creutzfeldt-Jakob Disease.

This is just a characterization of the antibody showing that the antibody specific to the

midregion of the protein and basically this is a Western blot analysis that we performed and this corresponds to cases of Creutzfeldt-Jakob disease and this corresponds to cases of scrapie in hamster and mice and this corresponds to a case of bovine spongiform encephalopathy and what we see is using this antibody that in cases with bovine spongiform encephalopathy there is an under representation of the nonlongated isoform.

So therefore, the pattern in the cow with bovine spongiform encephalopathy has a pattern of proteinase K resistant prion protein in the Western blot that is different from that we see in Creutzfeldt-Jakob Disease.

So I guess the very end of all this is what's coming up. So there are two main questions in prion research. One is how is the normal protein converted into the abnormal protein and how can we explain the phenotypic heterogeneity of this group of diseases?

I guess once again I want to leave you with a message that this is a heterogeneous group of disorders and that to perform a thorough surveillance analysis we have to look for the unusual cases. This work was done by a group of

people and most of the work was done by us in Indianapolis. The director of this group is Dr. Ghetti, the Director of the Division and also people in Milan and at New York University.

Thank you.

CHAIRPERSON CANADY: We're going to have questions now of Dr. Piccardo and I'm going to start out with one, which is, if you were going to surveil the donor for human dura what test would you propose be used?

DR. PICCARDO: Neuropathologic analysis you have to do a complete neuropathologic examination. A complete neuropathologic examination is to follow the CERAD methodology for Alzheimer's Disease. That means you have to perform -- you have to, of course, do a gross analysis.

And then you have to take sections from all of the different cortices from the cortex, occipital, temporal, basal ganglia, thalamus, hippocampus, cerebellum, pons, medulla. Perform conventional stainings, HME, staining for myelin, silver, etcetera and then, of course, you have to perform immunohistochemistry for prion protein. It's very, very critical to keep, if possible,

frozen tissue to perform Western blot analysis, molecular analysis and genetic analysis.

As you see, most of the cases are easy to diagnose. Creutzfeldt-Jakob Disease, any pathologist would make an analysis of a spongiform encephalopathy. However, we all have to be very well aware that cases that might look very much like an Alzheimer's Disease when we study them thoroughly, might not be.

CHAIRPERSON CANADY: Other questions from the panelists?

DR. EDMONDSON: Yes. Two questions, actually. Which one of these categories, the familial categories are infected?

DR. PICCARDO: First of all, a familial form is Creutzfeldt-Jakob Disease. And transmissibility has been shown in Creutzfeldt-Jakob in patient 200 and 178, for example, of course with sporadic occurrence, but you're asking about the familial.

German Straüssler Scheinker Disease has been shown to be transmissible from patient 102. There have been many attempts with Mutation 198 in the Indiana Kindred that has that assignment pattern and that's so far to the best of my

knowledge have been negative. But a negative in medicine is just a negative. We have to keep on trying.

Fatal Familial Insomnia hasn't been shown to be transmissible.

DR. EDMONDSON: Okay. In the clinical arena, not necessarily for just donors, but if neuropath specimens of cortex is submitted on patients who have Parkinson's Disease, or PCA or any neurodegenerative disease, would you recommend going through this check for prion?

DR. PICCARDO: If I receive a slide of the frontal cortex, for example, you're saying -- is that what you're telling me?

DR. EDMONDSON: Right.

DR. PICCARDO: Well, I mean, if there is a reason to I would perform because of my interest, of course, I would try to do a immunohistochemistry for prion protein because I was stuck many, many times with things at the beginning I thought were straight forward Parkinson and Alzheimer cases. Not many times, but it happened. So with my experience -- the cerebral amyloid angiopathy. With my experience, I would do immunohistochemistry for prion protein. Now with the odds of finding

accumulation of prion protein in the frontal cortex, for example, let's take Fatal Familial Insomnia. I mean the pathology there is mostly in the thalamus, not in any other area of the brain. This is another -- that's why it's important to have the complete brain for analysis.

When we have a biopsy, for example, the diagnosis is, for example, a report would be -- we do not see spongiform changes, etcetera, in the setting as specifics. What we talk about is that piece of brain. We cannot say what happens in another area. We know, I mean, looking at autopsy material that we section here and we do see nothing. We see nothing here. And then we section a little bit further and we start seeing spongiform changes. And we start seeing accumulation of prion protein. It's a complex deal.

Now if you're asking for 100 percent certainty, definitely, the only way to be 100 percent sure is to have the full brain and to perform a complete neuropathological analysis. There is no other way to get around this.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: Let's cut to the chase in the sense of finding out what's practical and what's

reasonable to do.

DR. PICCARDO: Yes.

DR. PENN: If you have a source where you know that there is no neurological disease by history and you have some neuropathology which maybe you can help us define that does not have any experimental procedures such as you do in your laboratory so well, how many cases of prion disease will get through and cause disease?

Are we talking about a diminishingly small number or is this a real threat?

DR. PICCARDO: I think it would be a very, very small number.

DR. PENN: So you would --

DR. PICCARDO: Clinically --

DR. PENN: If you were going to get a patch of dura put in your head for some reason, which we hope you don't need, you would be satisfied if we had good sourcing and general neuropathology at this moment with a provision that if a specific antibody test becomes commercially available that that could be done?

DR. PICCARDO: I would like to -- have to know that the donor had a complete neuropathologic analysis I would like to know --

DR. PENN: When you say "complete", you would mean all of those tissues?

DR. PICCARDO: I would mean --

DR. PENN: You would want to analyze it yourself for yourself --

DR. PICCARDO: Well, not necessarily myself.

(Laughter.)

I would like to know that the donor had a complete neuropathological analysis.

DR. PENN: Now we can say the same for AIDS by the way. What are the appropriate tests? We've just heard that AIDS is the bigger threat to patients, numerically, at least in the United States and so forth. So you might insist on having many more tests for AIDS than they're now doing. Is that correct?

Which do you think is the bigger risk?

DR. PICCARDO: Probably AIDS, I don't know.

DR. PENN: That being the case, we have to ask ourselves risk benefit analysis now.

DR. PICCARDO: Sure.

DR. PENN: And cost. And is there some reasonable grounds for going ahead and allowing

human dura out at all. Some countries have stopped it. Or is there a way of doing the screening that would be acceptable to your community, basically, that is still practical for people to do? These centers cannot spend -- if they spend over $1,000 say for doing neuropathology, it becomes something we can't use, clinically.

DR. PICCARDO: You understand that it's a difficult question because -- to answer. Because if you are asking me, well, you want certainty, 100 percent certainty, then the answer is --

DR. PENN: No doctor is going -- no practicing doctor is going to ask you for certainty.

DR. PICCARDO: If you want a reasonable -- if you want to say, well, we still take some risks, then there is no clinical history of neurological disease and you have some neuropathology and that patient did not receive dura grafts, did not receive

-- is not at risk, etcetera, etcetera, then probably will fall into a group of patients with -- would be pretty safe, I would say.

Now again, there would be no 100 percent certainty, I would say.

CHAIRPERSON CANADY: Other questions from the Panel?

DR. GONZALES: Can I just pose the question a little bit differently? Kind of reverse it a bit. Instead of putting the pressure, so to speak, on the medical community, yourself, to kind of answer the question of what's acceptable, shouldn't the question really be what is acceptable to the medical community, the population here in the U.S., government and then whatever that level of in quotes certainty would be, can the medically neuropathological and tissue collection system accomplish that and what will it take to accomplish that level of security and therefore can you gear up to provide us with that level, if you can?

Then is it possible to activate that sort of system, if you can't. Then to answer the question should we even be collecting dura grafts here in the U.S. Maybe it's not accomplishable. Maybe it's something that we shouldn't be doing.

So I would look at it from that standpoint. What is it that we, as a group of people, demand in terms of what is considered safe. Ask that question and then find out if the neuropathological community can, in fact, give us

that level of safety. If they can, is it feasible from a financial standpoint. If you can't, then maybe we should stop collecting dura.

And this should be asked of all the diseases, not just for the transmissible, but for HIV and other transmissible or infectious diseases.

DR. PICCARDO: Yes, I think that's right and at this time I know that a number of tests are being developed, so in due time we might have a diagnosis with new tests and then that will change again the whole thing.

DR. GONZALES: But again the question is what is it that the government, the people want to accept as a level of risk? That's the question that has to be, I think posed first in order for you to be able to answer these questions.

DR. PICCARDO: Sure and we can run a poll to see what kind of risk the general population wants to take.

DR. GONZALES: I'm not sure how we should do this. I mean I think that's the question that has to be posed first because that puts you on the spot to answer all of these questions about things that are -- I mean it's impossible to really answer with the clinical heterogeneity, the

pathological heterogeneity and the fact that there's an incubation period of decades, literally, with this disease that dura that is, in fact, infected, if you will, may be removed from individuals that are not expressing the disease, that's always going to be a risk. Therefore, it can never be 100 percent.

DR. PICCARDO: Absolutely.

CHAIRPERSON CANADY: Thank you very much, Dr. Piccardo. I want to just clarify for people in the audience who have come in since we began that we're completing the discussion from yesterday on the reclassification on human dura. I'd also like to introduce or have him introduce himself, Dr. Gatsonis, who has joined us.

DR. GATSONIS: Good morning. My plane made it through. I'm a statistician from Brown University.

CHAIRPERSON CANADY: Dr. Ku.

DR. KU: I have one question. Now in patients with absolutely a negative history of neurologic symptoms and no history or no evidence of neuropathologic abnormality on gross examination, it seems like you're saying that the risks should be reasonably low, but if there's any

sort of changes on the gross microscopy, then you're at a higher incidence. Is that correct? Of potential problems?

DR. PICCARDO: Let me see if I understand the question. You're saying a patient that did not have clinical science --

DR. KU: No clinical science and on gross examination has no obvious abnormalities.

DR. PICCARDO: And the microscopy shows pathology?

DR. KU: No pathology.

DR. PICCARDO: No pathology.

DR. KU: Would the risk be lower than -- significantly lower than a person with any sort of pathology? Can you do a screening test where if the patient has a negative history and a gross negative examination that you can say that these patients or these sources would have a relatively low risk?

DR. PICCARDO: Yes. If there is no pathology, no clinical history, etcetera. We fall back into, I mean a patient might be incubating the disease, the incubation time could be very long, up to 40 years. In Kuru, 16 years. In corneal transplants. We are dealing with a complex, very,

very complex issue, but to the best of our knowledge today, if we do not have any clinical records of pathological neurological disease, if we do not see any pathology after following your pathological examination, well, let us say that it is pretty safe.

DR. KU: So if you restrict your sources to that population, you can at least statistically reduce your likelihood?

DR. PICCARDO: I think that is correct.

CHAIRPERSON CANADY: I'm going to ask -- you can sit down. You've been standing a long time, Dr. Piccardo. Have a seat.

I'm going to ask for the purposes of the rest of our conversation if Dr. Durfor would put up the questions that were posed. I think that would refresh people's memories.

We're safe with Dr. Piccardo on the TSE Panel. He was loaned to us today and I think he served his function very well here.

DR. KU: I have one question for Dr. Malinin.

CHAIRPERSON CANADY: Go ahead. Dr. Malinin?

DR. KU: Your sources of dura, are those

patients candidates if they any sort of neuropathology or are they only candidates if there's a negative history and a negative gross neuropathologic exam?

DR. MALININ: Any donor with the neurological histories excluded from the donor pool and your donor with any evidence of degenerative diseases in the CNS is likewise going to be excluded. So the eventual diagnosis of Alzheimer's Disease versus other encephalopath is really of academic interest only because they would be taken out of the donor pool.

CHAIRPERSON CANADY: Thank you. Could you just summarize briefly the questions, Dr. Durfor?

DR. DURFOR: The questions asks you in addition to the guidance document which was in your briefing package, what other type of descriptive information could be included in a classification benefit -- thank you very much -- what other types of descriptive information should be included in a classification, identification for human dura mater?

CHAIRPERSON CANADY: Comments, panelists? Dr. Edmondson?

DR. EDMONDSON: Another question. Is there an advantage to human dura versus animal dura insofar as rejection?

CHAIRPERSON CANADY: I'm not sure rejection is much of an issue.

Dr. Penn?

DR. PENN: Well, they are different materials. Animal dura has different risks to it. If it's bovine, particularly. That might be a risk in how that's treated. And the material handles in a different fashion, depending on particularly how it's prepared. So there really are surgical differences in these different types of materials.

Neurosurgeons have been searching for the ideal material for a long period of time and human dura has stayed available, I think, in part, one availability, but also because it's met needs for a long period of time. If there was a perfect substitute of a synthetic material, we wouldn't have this discussion at all and they'd be out of business.

CHAIRPERSON CANADY: Most of the artificial materials are either difficult in the case of the Goretex graft for purposes of CSF

integrity or incite quite a bit of inflammatory response.

Other comments regarding this question from the Panelists?

The second -- you remember, we're going to be doing the end of this portion the sheet regarding reclassification.

DR. DURFOR: Question two draws upon your experience and medical knowledge to discuss any different uses or what limitations would you suggest for human dura mater devices. For example, an appropriate indication for use for the material is the first part of that question and the second relates to different uses with regard to surgical techniques to use the material and what limitations, if any, would you suggest for these different surgical techniques.

CHAIRPERSON CANADY: Any comments the Panelists would like to make?

DR. HURST: Everything that we've done so far has addressed the use of this as a dura substitute. Can anyone tell me a little bit about what other indications we might use? I know we saw a list of them, for example, maybe for heart valves or something like that, but I'm not all that aware

that as long as it's useful as a dural substitute that there should be any limitations on that. Maybe that's completely wrong, I don't know. Does anyone have any --

CHAIRPERSON CANADY: That would be my sense as well. I don't know.

DR. HURST: Okay. And the other question that I would have would be is there a necessity to put any restriction on the type of surgical technique that's used with human dura. It seems like the neurosurgeon who is going to be putting this is in would use the appropriate surgical technique in part B.

CHAIRPERSON CANADY: There's really not technically speaking much use for lay-on grafts unless you can't suture. It's a technique of last resort. In the future, we may have some techniques, but for now it's suturing, if you can; laying it on if you can't. So it's not a real distinction.

DR. HURST: Is there any need for us to mention anything about that?

CHAIRPERSON CANADY: I don't think so. I would agree with you.

DR. KU: Was there ever a technique of using cyanoacrylate glue for these grafts?

CHAIRPERSON CANADY: That's the future techniques I talk about.

DR. KU: Okay.

CHAIRPERSON CANADY: There's discussion about in the laboratory, but not a great deal in operative use for dura grafts. There has been some use for neuro -- for peripheral nerve suture.

DR. KU: I seem to remember they used to use IBCA for it, but apparently it fell out of favor.

CHAIRPERSON CANADY: Not currently.

DR. KU: Okay.

CHAIRPERSON CANADY: Next question.

DR. DURFOR: The third question runs along the same lines of the last question, but in this case we're questioning whether there were particular restraints on products' indication or use with regards to anatomical location.

CHAIRPERSON CANADY: My sense would be that they would not be, epiduras dura. Any other comments?

If we could then perhaps go on to the actual forms that we need to complete. As I recall

the process everyone gets an individual form and then we have a group form also.

DR. DURFOR: There's a fourth question.

CHAIRPERSON CANADY: There's a fourth question? Let's do that.

DR. DURFOR: This next question is something to consider while you are in the process of -- we hope you will consider as you complete the questionnaire that you are about to start and it deals first of all with the fact that the information that I provided to you yesterday with regards to clinical and technical problems associated with product use.

In specific, the questions are once again, based on your experience, have all the risks to health for the product been adequately identified? And this would be an aspect of Question 3 in the questionnaire. If not, what are the additional risks that should be described.

CHAIRPERSON CANADY: Any comments from the Panelists on this question? Do we have an overlay of the first form?

DR. DURFOR: The second part of that question follows up and asks have appropriate methods been identified to control the risk to

health for reach of the issues discussed in Part 4A and I have listed some examples. If not, what additional controls would be needed to control risk to health? And this relates to question 5 through 7 of your questionnaire?

CHAIRPERSON CANADY: Can we get clarification of what the discussion currently -- what the standards are now relative to donor screening, just that it's done or that it's done with certain exclusions?

DR. DURFOR: I think the most accurate reflection of how we believe it should be done was developed in the guidance document with reflect to the health and the recommendation provided with the TSE advisory committee. So what we have asked in that document is consistent not only with tissue bank standards, not only with what other human graft recipient -- human donor inspection would be for other grafts and then on top of that additional recommendations, given to us by the TSE Advisory Committee. And all of that is reflected in the guidance document that we have provided you which includes donor screening, donor evaluation of medical records and then some level of neuropathology.

DR. PENN: Do you specify exactly what level of neuropathology? Because that seems to be one of the problems here.

The other thing is the sodium hydroxide question, what evidence there is for that and I think those are contentious issues potentially.

DR. DURFOR: I would agree. I am just going to flip to the documents so that I say it correctly because I would hate to mis-speak.

DR. PENN: I don't remember exactly the words --

DR. DURFOR: It's on page 5, under 4. It talks about gross and histological examination of the brain. It talks about procedures for performing a full autopsy of each donor's brain. Brain, after fresh examination, brain should be fixed, sliced and gross examination of the entire brain conducted, including multiple cross sections and multiple samples of tissue obtained from different parts of the brain for histological examination. And we request that it's done by a qualified neuropathologist.

Does that answer your question?

DR. PENN: Do we have a qualified neuropathologist here? Can you tell us how long --

how much that involves? How expensive that is and whether you think that's a practical thing for every patient once they've been screened before dementia and the Central Nervous System Disease by history?

DR. PICCARDO: Regarding costs, I will have to defer the answer. I will have to do a thorough search on that, but we are talking let's say definitely under $1,000 to do that. But I would like to -- if you need a number --

DR. PENN: I don't need --

DR. PICCARDO: I'll be happy to give it to you later. I can check on that and come up with something that's realistic.

I think most of what has been described is appropriate. I don't know if it has been specifically described to perform immunohistochemistry for prion protein. I think that is important.

CHAIRPERSON CANADY: Is that widely available at this point?

DR. PICCARDO: It is available, I'm sure.

DR. PENN: It's an experimental procedure, is that correct?

DR. PICCARDO: Well, even by Western blot, the finding of abnormal prion protein on Western plot is not a diagnostic test as far as I know. However, we use it and we've relied on it when we put everything together. So everything that we have I think that we should use it and in this case to perform immunohistochemistry for prion protein is something that should be done.

The gold standard for this is this is commercially available and I think it has to be done. I would put a note there that in order to obtain the immunohistochemistry has to be done following hydrolated cortoclaven which is a special technique that has been standardized. Which is done in many different labs. It's not unique. It's not a secret and it's very sensitive. So I would include, on top of what has been said, to perform immunohistochemistry for prion protein using proper antibodies and techniques.

All that is published, is known and there are different labs in the U.S. that have the capability of doing that today.

CHAIRPERSON CANADY: Any other comments on Question 4? If not, if we could go to the overlay then?

Before we do that, one other question too. Do you have number 5?

DR. DURFOR: 4C.

CHAIRPERSON CANADY: 4C. Go ahead.

DR. DURFOR: And the last question, of course, is when during the premarket review of an application would it be appropriate to evaluate the performance of the device by some clinical data, some clinical evaluation before a product could be distributed commercially?

CHAIRPERSON CANADY: Comments? I'd like at this time to ask for any comments from the public, if anyone would like to make additional comments.

Please identify yourself and any relationship to any commercial product.

MR. PARDO: Hi. My name is P.J. Pardo and I'm with Tutogen Medical in Alatro, Florida and we're one of the manufacturers of dura in the U.S.

From previous meetings, it has been determined by neurosurgeons in the U.S. that they would like the availability of human dura upon their discretion. These guidelines make it almost impossible for manufacturers to perform that service to neurosurgeons and ultimately patients.

Total brain examination is impossible in most cases since collection of dura is not performed by a medical examiner. Routinely, the service is contractor to train personnel who does the collection of dura as well as other tissue material.

Histological examination as was explained by Dr. Piccardo is not standardized and it's not routinely available. The guidelines do not determine what a neuropathologist credential should be. Additionally, archiving of brain material for future tests, if available, poses a research use of material which is prohibited by many state agencies, not to mention the logistical and ethical issues associated with informing next of kin 10 years, 20 years down the line that there was some abnormality to what they donated.

In lieu of that, if we are going to continue to collect and process dura, these issues need to be addressed and we need to know what the panelists, as well as the FDA's, answer to these concerns might be.

Thank you.

CHAIRPERSON CANADY: Any questions from any other people who would like to address the

Panel from the public? We're going to close the open public session and go back to panel discussion. If we could put up the form on the overhead.

We go down this one by one, correct?

MS. SHULMAN: Correct. If everyone -- just a little housekeeping. My name is Marjorie Shulman. I'm with the Program Operations Staff. Please place your name on the top of it and everyone must fill out the form, but there will be one form for the entire group filled out by the Panel Chair.

DR. KU: I have one question for Dr. Penn and Dr. Canady. What are your surgical colleagues in other countries where they do not use human dura, what are they doing? Are they having any significant difficulties?

CHAIRPERSON CANADY: Well, it's interesting. My perception is that one of the most popular duras now, which is interesting in light of our discussion of prion disease is bovine pericardium. And then there are also artificial materials. Or you can use fibrous material from the patient themselves, but that prevents, causes some difficulty with scarring.

What's your perception, Dr. Penn?

DR. PENN: In Japan and England, they are doing without it, but I think there's --

DR. KU: Are they're having a significantly higher incidence of complications as far as leaks and other problems?

DR. PENN: It's totally impossible to tell because there's no data.

DR. KU: There's no data.

DR. PENN: There's no data.

CHAIRPERSON CANADY: The English have never much believed in closing the door anyway.

DR. PENN: That's right. There's a different attitude towards it and it probably, in Japan, it was overused. There was a huge number of cases of prion disease in those patients. That's the biggest cohort and there were an unusual number of cases when, in retrospect, where dura was being used. But I don't know how my Japanese neurosurgeons are coping with it.

CHAIRPERSON CANADY: It's always possible to obtain closure with something. The question is whether it's ideal.

Okay, we're ready to begin the sheet.

MS. WOJNER: Can I ask another question?

When patients undergo these procedures, just from a nursing standpoint, I know we ask them to sign informed consent about craniotomy. I can't ever recall hearing a conversation with a patient about this is a potential risk in relationship to the use of human dura. That's something you feel like should be added to that consent process or how do you think that should be handled?

CHAIRPERSON CANADY: It's not generally. I think it's accurate to say. You could argue that it is, could be, because interestingly enough the Red Cross now asks that question of patients. So I think one could make a reasonable argument that that should be something of certainly informed about.

DR. PENN: It's not high in our risk, 1 million to 1 is small compared to what we do.

MS. WOJNER: Sure.

DR. PENN: So in the same sense if we used blood in a procedure, we would not go down the whole list of --

MS. WOJNER: Well, actually, yeah, we do with blood. We have a whole secondary set of consents now that you've swept all the --

CHAIRPERSON CANADY: We don't.

DR. PENN: We don't in our --

CHAIRPERSON CANADY: Most institutions don't.

MS. WOJNER: Really?

DR. PENN: So it might be -- vary around the country as to what's considered. But patients don't read the consents with those things in mind when they're going to have a neurosurgical procedure. They want to know if they're going to survive and what the risk, major risks are.

MS. WOJNER: Sure.

DR. PENN: Not all these minor things. Lawyers, on the other hand, read those very carefully.

CHAIRPERSON CANADY: Other questions, comments? Then if we could start going down the form. Do we want to do this one by one and then vote on each issue?

MS. SHULMAN: Yes.

CHAIR CANADY: OK. Generic type of device processed human dura mater. Okay, the first question. Is the device life sustaining or life supporting?

Can we do it by hands with numbers, is that sufficient?

MS. SHULMAN: Certainly.

CHAIRPERSON CANADY: All that would say yes raise their hand? No? Can you raise them so I can count them? Eight?

One abstention. Let's do it again. Too many rules. 6 positive, I got 6 negatives, no positives and 1 abstention. Okay.

Number 2 is the device for use which is of substantial importance in preventing impairment of human health. Yeses raise your hands, please? Nos raise your hands, please? 6 nos, 1 -- did you raise your hand? 7 nos.

Does the device present a potentially unreasonable risk of illness or injury. All yeses, please raise your hand? Nos, please raise your hand? 7 nos.

MS. SHULMAN: Okay, in this case, number 4 is "did you answer yes to any of the above questions?" And that is a no, so we go to question 5. "Is there sufficient information to determine that general controls" -- general controls are the ones we went over yesterday -- "that general controls are sufficient to provide reasonable assurance of safety and effectiveness."

CHAIRPERSON CANADY: Class I level.

MS. SHULMAN: Correct.

CHAIRPERSON CANADY: All yeses, please raise your hand? All nos, please raise your hand. That's 7 nos.

MS. SHULMAN: Then we go to Question 6. "Is there sufficient information to establish special controls as a Class 2 to provide reasonable assurance of safety and effectiveness?"

CHAIRPERSON CANADY: Yeses please raise your hand? Nos please raise your hand? That's 5 yeses. 1 abstention, I believe.

MS. SHULMAN: Then we go to Question 7. "Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness. If yes, check the special controls listed."

CHAIRPERSON CANADY: What I'm going to do is read them this time. If you agree with this one and a yes, please raise your hand.

Post market surveillance? 7 yeses.

Performance standards? 2 yeses.

Patient registries? 6 yeses. Nos on that one?

Device tracking? 7 yeses.

Testing guidelines? 4 yeses, 5 yeses.

Let's do that one again. Testing guidelines, raise them high. 7 yeses.

Other things the panelists would like to see added to that?

DR. WALKER: Is donor tracking included in patient registries?

CHAIRPERSON CANADY: It was in the guidance document. No. Shall we say that?

DR. WALKER: If we want donor tracking, we need to say donor tracking.

CHAIRPERSON CANADY: Yes. All in favor of saying "donor tracking" please raise your hands. 6 yeses.

Other issues that people would like to raise under "Special controls"?

DR. PENN: I'm unclear. By voting this way, that doesn't mean we agree with all the guidance, the guidance document, is that right?

MS. SHULMAN: No, this is not voting on the guidance document, just the classification.

DR. PENN: Okay. I don't want an implication that because we're classifying, saying that there are things that should be done that we agreed with everything in the guidance document.

MS. SHULMAN: Yes.

CHAIRPERSON CANADY: Other issues people would like to raise under No. 7, special controls?

MS. SHULMAN: Okay, so 7 is a yes and therefore it's classified into Class 2.

Question 8, you all did say yes to performance standards so we'll answer this question. Performance standards are the ones recognized by rule making, but if a regulatory performance standard is needed to provide reasonable assurance of the safety and effectiveness of a Class 2 or 3 device, identify the priority for establishing the standard.

DR. WITTEN: Excuse me. Can I just have some clarification? I had thought that the group had said yes to registries, but not to performance standards.

CHAIRPERSON CANADY: That's correct. Performance standards were 2 yes, so it's a no.

DR. WITTEN: So it's a no.

MS. SHULMAN: Eight --

CHAIRPERSON CANADY: Since we don't want performance standards, we don't have to answer that, correct?

MS. SHULMAN: Correct.

CHAIRPERSON CANADY: For nine, for

device recommended for classification of Class 2, should the recommended regulatory performance --

MS. SHULMAN: That would be a no.

CHAIRPERSON CANADY: That's a no, too. Number 10.

MS. SHULMAN: Number 10 is only for Class IIIs. That is an N/A. On the back of the form --

CHAIRPERSON CANADY: Okay, "can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale distribution or use because any potentiality for harmful effects of the collateral measures necessary for the device is used." This is the prescription question.

MS. SHULMAN: Correct.

CHAIRPERSON CANADY: All who feel it should be prescribed? That's a backward statement, isn't it?

MS. SHULMAN: Yes.

DR. WITTEN: Excuse me. Can I just have clarification?

CHAIRPERSON CANADY: Sure.

DR. WITTEN: 11(a), that's not the prescription statement, right?

CHAIRPERSON CANADY: "Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use?"

MS. SHULMAN: By answering no, you're saying yes, it should be a prescription device.

CHAIRPERSON CANADY: Right, so all who would say yes on this issue, please raise your hand?

All who would say no? Seven.

MS. SHULMAN: So then we go to 11(b).

CHAIRPERSON CANADY: Then we identify the needed prescription. The choices are only upon the written or oral authorization of a practitioner licensed by law to administer the device, use only by persons with specific training or experience in its use, use only in certain facilities.

MS. SHULMAN: If I can clarify?

CHAIRPERSON CANADY: Yes.

MS. SHULMAN: It's not one or the other. They add on top of each other. So the first one is a regular prescription and then the other ones are additions.

CHAIRPERSON CANADY: Those who would wish that it would be -- require a practitioner

licensed by law to administer or use it, please raise your hand? 6.

Those who would like it used only by a person with specific experience or training, please raise your hand? 3.

All who do not feel that is the case, please raise your hand? 3 and I'm going to vote, 4 as the tie breaker. Negative.

All those who feel it should be used only in certain facilities, please raise your hand? All who believes it should not? 5.

You look confused, Dr. Piccardo.

(Laughter.)

The question is whether it should be restricted to certain facilities or not. Are you still confused or are you --

DR. PICCARDO: I suppose we could use it in special facilities.

CHAIRPERSON CANADY: We're presuming it will be used in medical facilities. I think this is restricted use of it within medical facilities.

MS. SHULMAN: I believe an example, some MRIs, that they're only used in certain facilities.

CHAIRPERSON CANADY: Right. So let's run that one again because it looked like there was

some confusion.

Those who think it should be restricted to specific facilities, please raise your hand?

Those who do not, please raise your hand? 7 nos.

So the conclusion would be this panel would recommend only on the written or oral use of a licensed practitioner.

MS. SHULMAN: Okay, now there's a second form to it, the supplemental data sheet.

Once again the generic type of device processed human dura mater. The Advisory Panel -- we'll fill that out. Neurology. Is device and implant.

CHAIRPERSON CANADY: Yes. Please, raise your hand? Go ahead. I'm doing something wrong.

MS. SHULMAN: No, I think it is an implant.

(Laughter.)

CHAIRPERSON CANADY: I was doing the process.

MS. SHULMAN: I like it. Indications for use. Does the Division have one? Do you have an indications for use?

CHAIRPERSON CANADY: Do we want to

restrict it within others in the utilization by a licensed practitioner?

MS. SHULMAN: Or make any changes to the existing one the Division has?

DR. DURFOR: These are the indications for which the current products have been cleared, so I would expect that we would ask you to consider these and if you feel they're appropriate, say so. If there are modifications that are needed, say so.

CHAIRPERSON CANADY: Comments from the panelists, please?

DR. EDMONDSON: For Item 4, if we restricted to certain specialties, does that mean that if the dura is found useful to close the pericardium or to be used in some other area of the body which would then involve various specialties, that would have to come back to the FDA for those uses?

MS. SHULMAN: It would be. It would be a new indication for use. It would have to come back in as a new 510(k).

DR. PENN: Can an ENT doctor do a neurosurgical repair of the dura?

MS. SHULMAN: I don't know.

DR. PENN: Certainly, orthopedists do. So I don't understand a neurosurgical repair means of the dura. I mean a repair of the dura done by anybody? Or does it refer to a board certified neurosurgeon doing this?

MR. DILLARD: This is Jim Dillard. I think that that tends to not be where the FDA gets involved, number one. Number two, I think earlier in your discussions for classification you did not restrict it to any particular specialties, I believe, Dr. Canady. So I think you should factor that in then to your indications for use and whether or not it needs to be even more general than these, in particular, to encompass other specialties that may be involved with human dura matter.

CHAIRPERSON CANADY: I think we ought to say it's for the repair of dura mater and whoever does it, does it.

DR. GONZALES: You don't want neurologists doing it as the wording indicates. I mean it's clearly neurosurgical and other surgical specialists, not neurologists.

CHAIRPERSON CANADY: That's what I'm saying. So let's say -- the indication would be

the repair of human dura. And the elimination of who does that repair? Maybe a robot next week.

Now under 5 it's the identification, is this additional risk other than the ones you noted? I think you had --

MS. SHULMAN: Yes, we can certainly say that as the ones noted in the panel meaning you can add to them or if you want to lay them out, that's totally --

CHAIRPERSON CANADY: Do you still have that overlay?

Would the panelists like to add anything to their perception of the risk? I take that as a no.

There are two sub components to that you might just look at under the specific hazards to health and characteristics and features of the device, just to draw your attention to that and make sure you have no comments on that portion either.

MS. SHULMAN: Number 6. Recommended Advisory Panel classification and priority, the classification is Class 2, and the priority is a high, medium and low and that's how quick you would like us to write the proposed regulation and the

regulation classifying in this device. High, medium, low.

CHAIRPERSON CANADY: Comment? Dr. Walker?

DR. WALKER: Hasn't this panel already 10 years ago assigned this a high priority?

(Laughter.)

CHAIRPERSON CANADY: You win.

MS. SHULMAN: We'll get right on that.

(Laughter.)

CHAIRPERSON CANADY: We'll do this quickly. Highs, one, two, three, four. Mediums, low? High wins.

We hate to get rid of the precedent.

MS. SHULMAN: Number 7. "If the device is an implant or is life sustaining or life supporting and has been classified in a category other than 3, explain fully the reasons for the lower classification with supporting documentation and data."

CHAIRPERSON CANADY: We decided it was not, so I think --

MS. SHULMAN: Well, as an implant, we can say, for example, the special controls can handle the risks and explain fully in the panel

discussion.

CHAIRPERSON CANADY: What was that? That was nice wording.

(Laughter.)

MS. SHULMAN: The special controls can handle --

CHAIRPERSON CANADY: Can handle. Okay.

MS. SHULMAN: Handle the risks and reasoning was discussed in the panel meeting.

CHAIRPERSON CANADY: And the final one is just summary of information that you've reviewed and we've reviewed, I would think today.

MS. SHULMAN: Right.

CHAIRPERSON CANADY: Is there a feeling, under number 9, the need for the identification of any additional restrictions?

MS. SHULMAN: And there is one from the previous one and that's, prescription device for No. 9 and then you can add any additional ones.

Okay, to the back of the sheet. No. 10 we can skip. No. 10 is N/A.

No. 11, existing standards applicable to the device, device subassemblies, components or device materials, parts and accessories. If we know of any existing standards, this is where we

could add those.

CHAIRPERSON CANADY: That's unclear to me. Do we need to add anything there necessarily?

MS. SHULMAN: No.

CHAIRPERSON CANADY: Any other comments from the Panelists on the forms? Then I'd like to take, if we could, a 10 minute break.

Oh, we need to vote on accepting the form. Okay. As completed, all in favor of accepting the form, as completed, please raise your hands?

DR. GONZALES: I'm sorry, we're having a little discussion here regarding No. 9.

CHAIRPERSON CANADY: Okay.

DR. GONZALES: And I just posed a question to Dr. Piccardo. In terms of identification of any needed restrictions on the use of the device, I asked the question will the restrictions that are present also be applicable to material that's obtained outside of the United States as there have been examples of transmission from foreign substances. So my question that we were discussing is that, are the restrictions that are placed on foreign companies at the present time the same restrictions that we have or proposing

that we have with processed dura mater here in the U.S.? And I'd like to ask Dr. Piccardo if he's familiar or anyone else, if they're familiar with the restrictions and if those restrictions are similar to the restrictions that we have here in the U.S. That would be --

CHAIRPERSON CANADY: Let me start a further question. That is, if we state within the form that these are the restrictions that are necessary, these are the conditions that are necessary, would that apply to foreign as well as U.S. obtained dura?

DR. WITTEN: Anything that you recommend in terms of special controls will apply to any product that was marketed here under that classification and I just want to clarify that actually No. 9 is about the use, restrictions on use, not restrictions on acquisition of raw material or of the dura.

DR. GONZALES: Is there any place we can say anything about acquisition?

DR. WITTEN: You can say it where you recommend, I think it's number 7 where you talk about what kind of controls -- isn't that where -- No. 7. You can just add any other recommendations

you have about what you think because that's where you're describing why you think that it can be safely used or safely -- yes, as a reasonable product for this classification.

So you certainly would feel free to put this information in under the question.

DR. PENN: I'd like to make two points in regard to this. Number one is that there has been an additional case from Germany, as I understand it, of tutoplast causing prion disease, that has occurred just recently. Is that correct?

That's my understanding. The other thing is that in the last -- I think I'm the only survivor of that last panel meeting a few years ago. I was presenting at least, at that meeting and at that meeting they were talking -- people in the United States were talking about harvesting dura from Eastern European countries and that they would have to put the information about it, translated into Croatian or whatever they were going to do. And we were all upset about the possibility of bringing in dura from other countries and processing it in the U.S. and selling it as a U.S. product because we felt that it would be extremely hard to get controls for that. And I

don't know how to phrase it such that we are assured that the standards being used in foreign countries are exactly the same as here, for any of the material that is sold from the United States.

CHAIRPERSON CANADY: Mr. Dillard?

MR. DILLARD: Yes. Jim Dillard. I think in context to what you're doing here which is giving us a recommendation for Class 2 on this product, that if anybody wanted to do that, bring dura in from another country, process dura either here or there, they would be required to get premarket clearance from us, the Class 2 kind of clearance through a 510(k) that you're recommending and in order to do that they would have to submit a 510(k) to us which we would review. Contained within that review procedure, I think just the issues that you're bringing up are the types of review issues that we bring up with a manufacturer or with an importer or with a distributor before they would get clearance.

So a lot of that is contained within the 510(k) review process, the Class 2 review process and so I think your recommendation and just your discussion is enough to really highlight to us what some of those important things are for us to

concentrate on in our review process.

DR. PENN: Would that apply to things that -- I don't know whether companies are doing that today that are already supplying it in the United States. Would that same hold for them?

MR. DILLARD: Part of that also would be captured in the quality system regulation and when we would do inspections, so the sourcing of the material, etcetera, would be something that we would look at from an inspectional point of view.

CHAIRPERSON CANADY: Any other comments that the panelists would like to make?

Dr. Gonzales?

DR. GONZALES: If the restrictions are being made for a level of contagion that has been determined to be at a specific level for tissue controlled in the United States, and those restrictions are then applied to tissue collected outside of the United States that may have a different level of contagion, it would seem to me that the restriction should reflect where that tissue is being collected and not assumed to be for tissue that's collected at a certain contagion rate. If the numbers we're using in terms of the contagion are those for the United States, and all

the restrictions that are being created here and all the methods of processing, even if we then impose these same restrictions on foreign tissue, if, in fact, the contagion rate is higher or much higher, then it would seem to me that the restriction should be tailored to the countries from which this tissue is being obtained.

To make the assumption that the contagion rate is going to be exactly the same as here in the United States I think is wrong. To give you an example, to have restrictions that, let's say for AIDS at a certain rate that it is here in the United States, would not be the same as the contagion let's say in Rwanda or South Africa. And if tissue is being collected from those countries, the restrictions and the methods of collection and preparation may not be sufficient. That's my concern right now.

I don't know, I mentioned earlier that there's one, for instance, I think Dr. Piccardo can address this better, but there are groups of patient populations where, for instance, in England or in Libya where the incidence is 30 times higher of Creutzfeldt-Jakob Disease that in those patient populations you may want to have a different set of

restrictions and that's what I'm saying right now in terms of caution regarding this application worldwide to our restrictions which are tailored specifically to the contagion rate here in the United States, is my understanding. This is not being, is not taking into account the possible contagion level for other countries.

Now it may be that the restrictions that we have are more sufficient. I'd like to hear that, that in fact, the restrictions that we have and methods to protect the public are more than sufficient for any country anywhere in the world. That may be the case. I am just not familiar with that. But I would like to hear more about that and until we have more information about that, I'm hesitant about saying that there are no other special controls in 7 here that shouldn't be applied to other countries where we know the contagion rate is higher.

MS. WOJNER: Can I add something to that?

CHAIRPERSON CANADY: Yes.

MS. WOJNER: I think if you take into consideration how small a planet this has become and the latency periods that were discussed, I hear

what you're saying and I agree with what you're saying, but it's probably impractical to even suggest that there is one contagion standard for just the United States.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: I think really when we consider regional differences for these infections that we should identify the high risk areas and just eliminate those as donor pools.

CHAIRPERSON CANADY: Do we wish to go back to 7 and add that to as a restriction, special restriction? No donors from high risk areas?

MS. WOJNER: I'd like to hear what Dr. Malinin --

CHAIRPERSON CANADY: Dr. Malinin --

MS. WOJNER: Would say with regard to that.

DR. MALININ: Well, Dr. Solomon can probably address that particular issue. The CDC identifies high risk areas. I'm not familiar with the encephalopathy areas, but I certainly am with the HIV infections. And the general voluntary standards are not to accept donors from high risk areas, particularly for AIDS.

Now these have never been enforced and

it is a possibility including areas in the Caribbean from which the tissues have been obtained from donors. This is within the United States, but the areas are clearly identified where there is a high risk.

Now with HIV, of course, there is very extensive testing. And the problem with HIV is not elimination of the donors with the disease itself, that's very easy to do, but elimination of the donors which may be potential carriers and unrecognizable.

The last time we have looked at this and the American Academy of Orthopedic Surgeons has addressed that particular issue specifically and put out the guidelines on it, the chance of us having a donor unrecognized who may have HIV infection is probably a little more than 1 in 2.5 to 3 million was the PCR.

Now if you implant tissue from such an unrecognizable donor there's an additional chance because you're running a chance of 1 in 250 or becoming infected. This is the same infection rate as the surgeon who would have a percutaneous injury while operating on a patient with AIDS.

So there have been safeguards and there

certainly has been information donor-wise, but I think FDA has specific criteria having to do with any tissue donors and I think this is probably the area that would address that particular issue where they can put out additional guidelines saying that these donors would not be acceptable from a particularly highly indigenous area for a particular type of a contagious disease.

If Dr. Solomon could comment on that because she's in charge of that particular --

CHAIRPERSON CANADY: Dr. Solomon?

DR. SOLOMON: Hello. I'm Dr. Ruth Solomon, FDA, CBER. I'm Director of the Human Tissue Program. As you heard earlier yesterday, we are considering the possibility that human dura mater could become what we call a 361 tissue, that is, it would be regulated under Section 361 of the Public Health Service Act which specifically targets the transmission of communicable disease, the prevention of transmission of communicable disease.

We currently have a final rule in place and a guidance document that deal with human tissues intended for transplantation of which dura mater is not one of those. Those tissues would

include bone, ocular tissues, skin, musculoskeletal tissue, in general.

We believe in answering the point made earlier that the current donor screening and testing requirements contained in the final rule are sufficient to weed out high risk donors. In other words, previous to having a test for HIV-2, for instance, FDA had a recommendation to defer blood donors who were from Haiti and this policy was considered quite discriminatory and as soon as a test was on the market for anti-HIV-2, an FDA licensed test, the exclusion of blood donors from Haiti was eliminated.

Rather than targeting specific regions of the world, I think the thinking is that if we look at donor screening and look at certain high risk behaviors and defer donors who have those high risk behaviors and also perform testing. For instance, the current required testing is for HIV-1 and 2, hepatitis B and hepatitis C, that that is sufficient rather than targeting specific regions and one could argue that, for instance, we do not in the United States say that you cannot collect from intercity areas, for instance, for blood and tissue donors where we know that the prevalence of

certain diseases is higher than in the general nation. Again, because we feel that the controls in place through donor screening, looking at particular high risk behaviors are sufficient rather than using a regional approach.

CHAIRPERSON CANADY: Can I recommend for consideration to the committee that since we don't have a specific screening for prion disease at this point that we might want to specifically at this point exclude the areas known to be high, at great risk for prion disease.

DR. SOLOMON: Excuse me, could I just add another thought? You may be aware that for blood donors a recent guidance document has come out that would defer blood donors who have resided in or visited the U.K. between 1980 and 1996 for a cumulative period of more than 6 months. However, before -- and that was a recommended of our Blood Products Advisory Committee, but before they recommended that, they had the industry go back and look at the impact on the supply of blood that such a recommendation would affect and in the tissue area we have been asked are you going to apply the same U.K. restrictions to tissue donors and our answer has been no, again, because we don't know

the influence that would have on the supply of tissues and I think you should be cautious when you make a recommendation such as that. You have to factor in the effect that would have on supply.

CHAIRPERSON CANADY: Yes. I think we are being cautious, but I have that that's the sense of the panel, that they really have that concern. We can see whether that is a wish or not and we can resolve the issue that way.

Is there a wish to include a concern about donor side or not? Can we raise hands on that? Yes? No? So the wording I would propose is that pending screening tests for prion disease that donors be restricted from the known areas at epidemiologic risk. Would that be reasonable wording?

MR. RHODES: I'm sorry. Epidemiological risk of what?

CHAIRPERSON CANADY: Of prion disease.

MS. WOJNER: Point of clarification, do we also need to go back to then that first form and fill that in under No. 7 there where we had added donor tracking?

CHAIRPERSON CANADY: That's where we're going.

MS. WOJNER: Okay, so both sheets.

CHAIRPERSON CANADY: Right.

DR. SOLOMON: Sorry to be making a pest of myself, since you did go back to No. 7, could you please clarify what you mean by "donor tracking" because these donors are dead for the most part.

(Laughter.)

CHAIRPERSON CANADY: I forgot who added donor tracking? Dr. Walker.

DR. WALKER: Yes.

CHAIRPERSON CANADY: Could you clarify?

DR. WALKER: Tissue -- who were they, what were their medical histories and what do their brains look like?

CHAIRPERSON CANADY: Okay. Other questions?

Having made that amendment I guess we should go back and vote on the first form at this time and the form, as completed, if you could review -- do you have one that we completed?

MS. SHULMAN: Yes, I believe Steven does.

CHAIRPERSON CANADY: So you can see how we completed it. And with the addition of the

statement that we made regarding epidemiologic risk, all that would agree with the form as completed represents the Panel's opinion, raise your hand, please?

I see 7 yeses. Nos? Form 1 is complete.

So we've completed the recommendation regarding the classification of human dura.

Do you have anything else that we need to do?

MS. SHULMAN: No. Do you want to vote on the supplemental sheet?

CHAIRPERSON CANADY: She said we didn't have to.

We'll vote on the supplemental sheet.

MS. SHULMAN: Just on the whole thing.

CHAIRPERSON CANADY: Raise your hand if you agree with the supplemental sheet? All those who disagree raise your hand?

I'd like to take a 10 minute break and then we'll begin today's work.

(Off the record.)

CHAIRPERSON CANADY: I'd like to call the meeting back to session if I can get everybody sitting down again.

We're going to reconvene and this portion of the meeting will be discussing the draft guidance for neurological embolization devices. I'd like to open to public hearing.

I understand there's one scheduled speaker. Mr. Kevin Daly, if you would identify yourself and your interests.

MR. DALY: Thank you. My name is Kevin Daly. I'm the Vice President of Regulatory Affairs and Quality Assurance for Micro Therapeutics in Irvine, California. We're developing a line of liquid polymer embolic compounds.

I just have several comments that I'd like to make on the guidance document and would like the panel members' response. The first question I have to ask for comments is regards the adequacy of animal data in lieu of clinical data and I'd like to just pose something to you. Assume that a new permanent implanted embolic material is tested in animals under simulated use conditions and it's shown at one year to be non-histotoxic, stable and otherwise shows a normal healing response. Would the panel agree that threshold PMA submission and approval requirements may be limited to 6 month imaging assessment, for example,

angiography, MRI or CT, etcetera?

Further to that, if the Panel believes that longer term, that is greater than six month assessment is needed, that such follow up data may be collected via a post market surveillance program.

Madam Panel Chair, shall I read through each of my questions or will there be a response to each?

CHAIRPERSON CANADY: At this time there will be no responses.

MR. DALY: Okay. So perhaps power failure, huh?

(Laughter.)

Section 9(a) of the guidance document lists a number of safety endpoints for which data is to be collected. However, the document does not differentiate between those end points which may be bundled, if you will, to represent a primary study endpoint and those which may be defined as secondary study endpoints. And this truly is a statistical sort of issue and question. The concern is that for the purpose of defining study sample size and study hypotheses, the less important endpoints may be inappropriately weighted

the same as those which are most important. It's recommended that the guidance document should recognize that the most important endpoints may be bundled to form a composite primary safety endpoint while all others may be defined as secondary endpoints.

Thirdly, for presurgery embolization patients, please comment on whether angiographic reduction in tumor or lesion size is an adequate surrogate endpoint for surgical blood loss as a primary efficacy endpoint. Stated differently, for the purpose of evaluating new, neurological embolization devices, is it reasonable to contend that angiographic reduction in tumor or lesion size is a more concise measure of whether the embolization material is suitable for its intended use, that is, of being a vascular occlusion device than is blood loss which is subject to the variabilities of tumor size, location or complexity or surgical technique that may affect such measurements?

A minor point for FDA or the panel, given the panel members are experts in their field, they may be interested in participating in clinical trials. Does a panel member's participation in a

clinical trial affect their ability to vote or comment upon a PMA which may come before the panel for review?

CHAIRPERSON CANADY: For that answer, we'll say yes.

MR. DALY: It does affect their ability?

CHAIRPERSON CANADY: Yes.

MR. DALY: Okay. Lastly, I'd like to applaud FDA for developing the guidance document. It's especially useful for manufacturers that are developing new embolic devices because it helps eliminate confusion over the premarketing requirements.

CHAIRPERSON CANADY: Thank you very much, Mr. Daly.

MR. DALY: Thank you.

CHAIRPERSON CANADY: Any other public comments?

We'll now proceed then with the Open Panel Session. I would remind the panelists, please speak into your microphone so the transcriptionist's job can be made easier.

Dr. Foy, are you going to present?

MR. FOY: Good morning. My name is Keith Foy. I work for the -- I'm a reviewer with

Plastics and Restorative Branch. This morning we'll be discussing the guidance on neurological embolization devices. The CFR describes an artificial embolization device for neurological use as an object that is placed in a blood vessel to permanently obstruct flow to an aneurysm or other vascular malformation.

At the June 12th meeting the panel considered the information in three 515(i) submissions of safety and effectiveness information on three types of neurological, artificial embolization devices. They were the PVA particles, detachable balloons and coils. They recommended that these devices be reclassified to Class II for the indications of "... to permanently obstruct blood flow" -- I need a little light -- that's fine. "Blood flow to an aneurysm or other vascular malformation", not excluding hypervascular tumors.

At this meeting, the panel cited biocompatibility and labeling as issues that special controls should address.

(Laughter.)

That's good. One of the ways we address special controls is through the use of guidance documents. These documents assist companies and

FDA in the review of a device.

The neurological embolization guidance document contains intended use and indications section, a device description, preclinical testing, biocompatibility, animal testing, clinical testing and labeling sections.

The intended use and indications section has been provided to give examples of the PVA particles, detachable balloons and embolization coils.

The device description section briefly lists the contents of a complete device description.

The preclinical testing section was broken down to provide specific comments on each device, including polymeric embolic agents such as the cyanoacrylates. Comments on device component interaction and shelf-life were also provided.

Biocompatibility testing section provides a list of applicable tests, cites additional tests that relate to devices that remain in the body for greater than 30 days, and refer the reader to other relevant guidance documents.

As animal testing may be appropriate, the guidance provides a brief list of issues that

any animal study should address.

Also, because the agency believes that some devices, for example devices that use a novel detachment system or represent a new process of embolization, may need clinical data to support a regulatory decision, the clinical data section contains comments on specific issues regarding the design and analysis of clinical trials.

Lastly, the guidance document provides comments regarding labeling for these devices.

When considering the guidance document, we'd like you to consider the following questions. Instead of reading each question verbatim, I'll summarize the intent of each question. Question 1 asks you to consider the assessment tools used in clinical trials and to comment on these.

Question 2 asks you to consider the appropriateness of the different imaging tools that are used and which ones are available.

Question 3 asks you to comment on study bias.

Question 4 asks you to comment on clinical measurement tools.

Question 5 asks you to comment on collateral vessel formation.

And the last question asks you to comment on long term follow up.

CHAIRPERSON CANADY: Any other FDA discussants?

Dr. Ku is the lead discussant for the panel itself. Oh, I'm sorry, industry? There's an industry presentation. Coordinate it. Thank you.

If you would identify yourself and your affiliations.

MS. WEBB: Sure. Does everyone have a copy of the new handout that they gave, that we brought in? It's a redline copy of the guidance document?

CHAIRPERSON CANADY: Yes.

MS. WEBB: Okay.

CHAIRPERSON CANADY: It was handed out during the break?

MS. WEBB: That's correct.

CHAIRPERSON CANADY: And it has industry comments and underlined areas on it, if you -- just for the panel's help in finding it.

MS. WEBB: There are more on the table outside, if the audience needs some..

CHAIRPERSON CANADY: It's on the table outside for other people.

MS. WEBB: On behalf of Boston Scientific Target, the Cook Group Companies and Cordis Endovascular Systems, thank you for this opportunity to speak and to provide you with our perspective of the guidance document being discussed today.

My name is Lisa Webb and I'm representing Cook, Incorporated. Remarkably, we have three other people who made it through the torrential winds yesterday and actually made it here, that is Isabella Abati and Roxanne Baxter from Boston Scientific Target and Lisa Wells from Cordis Endovascular Systems.

Our team has reviewed the proposed guidance document for neurological embolization devices and has several comments which we believe will provide additional clarity and eliminate redundant testing.

Those are a few of the products we have.

We support the down classification of these artificial embolization devices to Class 2 and it is our understanding that this guidance document may serve as a special control.

We have submitted a redline copy of the document which includes suggested changes for the

official record. We will not review all of the changes and suggestions we made in the redline copy, but we would like to present a few of the most important recommendations to the panel for discussion today.

To begin, we have a few general comments regarding liquid embolic agents such as cyanoacrylates. We respectfully request that these embolic agents be excluded from the scope of this guidance. We request this because liquid embolic agents will mostly likely remain Class III devices and will require PMA. The documentation needed to support a submission for liquid embolics will likely differ from that of other devices in this guidance document.

And now if you would like to follow along with me, I'm going to refer to different sections in the redline copy, starting with Section III.

CHAIRPERSON CANADY: I might just say, ours is black line.

MS. WEBB: Okay, black line. I'm sorry. That would be more correct.

So Section III of the guidance document concerns regulatory classification. And this is

sort of another general comment. It's our understanding that the language for CFR subsection 882.5950 and product code HCG will be amended to include a statement such as "these devices include PVA particles, detachable balloons and embolization coils."

Moving on to Section IV, we believe that the indications for use for neurological embolization devices should not be limited to presurgical use. There are already 510(k) cleared devices on the market which do not have this limitation. We therefore request that this limitation be removed from the examples of indications for use.

In Section V titled Device Description, you will notice that we have proposed several changes which will eliminate redundancies covered in other sections of the guidance document.

We have several comments regarding the preclinical testing requirements of Section VI. First, we believe that the development of preclinical testing protocols should be based on the QSR risk assessment for the specific device. The requirements necessary will depend greatly on the risk analysis associated with the specific

material. Issues specific to the particular device and delivery system will differ. Therefore, the manufacturer, in consultation with the Agency, may add or substitute tests described in the guidance with adequate justification.

Second, cyanoacrylates and embolic agents other than PVA, coils or balloons should be categorized as liquid rather than polymeric embolic agents. Technically, PVA is a polymeric agent since it consists of varying links of polyvinyl alcohol chains. Additionally, not all liquid embolics may polymerize. Liquid embolics are materials that are delivered as liquids to the embolization site, undergo a phase change in vivo and activate into a physical mechanical block or embolic device. We request that liquid embolics be defined as such in the guidance document.

Third, final release criteria specifications for PVA, in other words, particle size, amount of particulate, color, fill volume, et cetera will demonstrate that appropriate controls are in place to insure the intrinsic safety of the product. Additionally, biocompatibility testing will address the presence of processing additives and contaminants, including formaldehyde.

Biocompatibility is already covered in Section VII of this guidance document.

Fourth, historically, it has been acceptable to propose shelf life based on a test protocol using parameters representing expected storage conditions, acknowledging that confirmatory real time testing is sometimes needed. We request that the guidance language in this section be slightly modified accordingly.

We have only two comments on Section VII which covers biocompatibility testing. First, a listing of all the required testing is not necessary, given that the guidance document recommends adherence to ISO 10993.

Second, we believe that biocompatibility testing should be permitted on samples formed from finished sterile devices.

Moving on to Section VIII, animal testing should be conducted only when appropriate bench testing and in vitro models are unable to address product concerns. Issues such as local and systemic foreign body reactions and infection that are listed in this section of the guidance document are addressed previously through biocompatibility testing as outlined in Section 7.

Section 9 addresses clinical data. We believe that clinical evaluation should be required when the safety and effectiveness cannot be determined through nonclinical testing. Additionally, the need for clinical data to support design modifications to coils, balloons, PVA or deployment mechanisms is expected to be rare.

In the rare instances where clinical data may be required to address safety and effectiveness issues, the trial objectives and endpoints must be carefully considered, given the complexities associated with treatment of this patient population. The primary objective of clinical data is to assess the ability of the device to perform its intended use which is to obstruct blood flow to the targeted site. The endpoints and success/failure criteria must be consistent with this intended use.

Patient treatments are highly specialized with different goals and may involve the use of several different types of embolic agents. Given the low incidence and prevalence of these disease states and the limited number of neurointerventionalists performing these procedures, the use of historical controls appears

to offer the most practical means for assessing device performance in terms of patient outcome and complication rates.

And this is sort of an addendum now that I've heard Keith's speech this morning and he pointed out in Question 6, I believe, that FDA is looking for one year follow up on clinical data. We'd also like the panel to discuss that very carefully.

We believe that with the use of these clotting devices, embolization occurs very rapidly. I think my understanding is that within 24 hours of embolization, clotting occurs. And for industry, we believe that one year is -- one year follow up from clinical trials is overly burdensome. Historically, the clinical trials that have been performed on these type of devices do not require this length of clinical trial follow up.

Okay, moving on, continuing with Section X, titled labeling, we have omitted some redundancies from this section. We believe that these omissions are appropriate because references are already made to CFR labeling requirements and several FDA labeling guidance documents adequately cover this subject.

In conclusion, we would like to thank you for the opportunity to speak today. This presentation was intended only to raise the most important issues that industry has in terms of this guidance document. We ask that you review the black line copy of the guidance document for an understanding of our changes. The changes should be pretty self-explanatory and those that aren't, are annotated.

It is of the utmost importance that the Panel recognize that this guidance document applies primarily to devices that will be Class 2, that is down classification for these types of devices has already been recommended.

Therefore, it is expected that special controls are sufficient for regulating these types of devices and that clinical data will typically not be necessary. Thank you.

CHAIRPERSON CANADY: Thank you. Are there other speakers with your presentation?

MS. WEBB: No, we worked on this together and the red line or black line copy comes from all of us.

CHAIRPERSON CANADY: We have -- this is not a time for open comment.

Are you a part of this group of representatives? Then we're going to thank you very much and go on to the Open Panel discussion.

Dr. Ku was the primary reviewer for the Panelists.

DR. KU: Madam Chairman, fellow panelists and guests. Thank you. Thank you for this opportunity to review this guidance document for neurological embolization devices. As Lt. Commander Foy has presented, there's been a large body of studies reporting the usefulness of these embolic devices in the treatment of a variety of vascular lesions and hypervascular tumors.

It's important to recognize that many embolic devices have been in existence for 20 to 30 years and that operator skill is one of the major determinants in the safety in the use of these devices. A number of major improvements in treatment results have also resulted from improvements in delivery devices, not just the devices that are embolic agents, as well as changes in operator training.

I agree with industry that liquid embolic devices probably should remain Category 3 and 1 think it was stated on the guidance document.

Three is also on the horizon use of particulate embolic agents that operate on mechanisms of chemotherapeutic action and potentially genetic transfer. And these may be either coded on the embolic devices or chemically bonded. These devices are not well studied at the present time and operate on alternate mechanisms of action other than direct occlusion so that these devices obviously should not be included on this particular guidance document.

However, this guidance document overall as far as many of its parameters may provide some utility for industry in considering submitting liquid embolic agents or these newer types of bio-active or genetically active embolic agents in that it does provide a general framework so that while it doesn't specifically apply, I think that we might consider that if there is a guidance document for future embolic agents that many of these parameters should be considered.

Do you want me to assess, go item by item as far as the questions?

CHAIRPERSON CANADY: I think you might as a beginning point for our conversations, yes.

DR. KU: Okay. For the first item as

far as outcome scales and clinical evaluation, probably the most commonly used ones are probably NIH Stroke Scale and the Barthel Index for Long-term Function. Obviously, this is probably going to be different from institution to institution and locale to locale. But these standards are all pretty well recognized and I would probably ask one of our neurologists here as to what is the most appropriate for a given situation.

In general, the complications that occur from embolization are ischemic events or stroke. Most of these events are acute events, so that that would be the type of scale that you would be looking for. You would be looking for an acute injury and then the long-term outcome and recovery from any untoward complications.

As far as imaging tools for clinical studies, angiography has certain advantages in that it provides structural detail as to percentage of AVM or tumor successfully occluded. It has an advantage in that it provides flow information as to how much flow there is to a particular lesion. The obvious disadvantage is that it is an invasive test and there are risks associated with performance of the test.

MRI, MR angiography and CT are all relatively noninvasive other than the use of contrast which is a relatively minor risk. The disadvantages of that, it does not provide accurate flow data. MR angiography will provide gross flow data, but it will not tell you what the actual flow rate is. It will tell you whether there's significant flow or not significant flow.

MR and CT will provide significant information as far as structure, especially with regards to tumor because you can use contrast to determine what part of the tumor has been devascularized and what part is still receiving what.

Angiography may not provide that detail for tumors.

For AVMs or fistulas, angiography is probably superior because it has higher definition and detail.

With respect to reader bias and review of data, there is, obviously, a certain utility to use of centralized reader or readers. It doesn't eliminate bias, but it reduces variability on the interpretation of results. Whether a study is blinded or not, it provides a little bit of

additional statistical power. Probably, the most important studies are basically the pre-procedure angiogram or MR or CT as compared to the immediate post-procedure angiogram and/or CT as far as radiographic evaluation of the success or percentage of occlusion of a particular vessel or vascular bed.

As far as pre-embolization patients, traditionally surgical time and blood loss has been the traditional way of evaluating this. Another way of evaluating it is the surgeon's opinion as to their extent or completeness of reception of either AVM or tumor because that's the ultimate outcome that you're looking for.

The industry comment as far as angiographic evaluation is also certainly a very valid point because the thing that you're looking at as far as determining degree or successfullness of occlusion of a vascular bed is going to be your angiogram and three are certain factors which will influence how complete that occlusion is, depending on when surgery is done. If it's done immediately after the embolization procedure or if it's done in a delayed fashion where you could have collateral formation which is addressed in the next item.

For things like AVM, if it's a presurgical embolization, typically, these -- the surgery is done very soon after the embolization so there is no opportunity for collateral formation. The same thing is true for tumors.

Now if you have a very large AVM or a very large tumor that requires staged embolization, obviously what you want to do is you want to consider the last angiogram done immediately before the surgery as your endpoint as to how successful you have been in occluding the vessels.

If it's going to be a lesion, such a brain AVM where you're going to be considering stereotactic and radiotherapy, or a tumor where you're going to be considering radiotherapy, then the effects of those treatments are not immediate. In general, they're delayed, so there, you may need long-term follow up either with angiography or MRI. And in those situations, in things like AVM, the follow up is typically up to two years for radiosurgery. The reason is it takes up to two years for full effect to take place. So that has to be evaluated on a lesion by lesion or disease by disease category basis as to determining what the appropriate length of follow up is.

Now whether or not that follow up needs to be paid for by the industry protocol or not, I am not sure. The reason is because these follow ups are actually standard, clinical care. So if you have a brain AVM and you have embolized it and the patient's been treated with radiosurgery, you can include it as part of the clinical protocol or the research protocol or you could take the data that will be obtained anyway two years down the road to assess for the degree of completeness because that data will have to be obtained for clinical reasons to determine the degree of success of the procedure.

As far as the types of follow up and the appropriate time intervals, I would recommend up to two years for brain AVMs. Angiography probably should be done as a last study or at the two year endpoint. The reason is it's the most sensitive for detecting small collateral vessels or recurrent or residual AVMs.

MRA or MR angiography is less sensitive. It can be used as a screening exam between the beginning of the procedure and the endpoint. As far as tumors, I think MRI or CT are both sufficient for evaluation and that's actually been

the way that most residual tumors or recurrent tumors are followed, with MRI or CT.

CHAIRPERSON CANADY: Thank you very much, Dr. Ku.

Dr. Foy?

MR. FOY: What was the time frame for the tumors?

DR. KU: For tumors, that depends on the type of tumor. Very often patients with meningiomas are followed for a couple of years to make sure that they didn't leave any residual. Typically, they will get a study at a year or two years and if there's no recurrence, then that will be the end of the

follow up, but that's a clinical type of study.

As far as the effectiveness of the embolization agent, I don't think it needs to be that far out because you're only looking for an immediate effect with respect to the surgery.

CHAIRPERSON CANADY: Sally's ready to start the free for all.

MS. MAHER: Dr. Ku, I think what the FDA was maybe looking for was some idea as to what length of follow up they need to see in order to approve or clear the device and I think you're

talking about two different things.

DR. KU: Correct.

MS. MAHER: I'm wondering if maybe the industry was correct, we should be looking at maybe a six month follow up time for the clinical studies to get on market, but there are other issues that have to do with the medical treatment of a patient that are outside of the approval process.

DR. KU: That is correct. I agree. That's why I'm saying that you may consider even a shorter endpoint for the immediate angiographic effect because if the surgery is going to be done a week after the embolization, that's your endpoint.

CHAIRPERSON CANADY: I'd like to entertain general comments from the panel regarding the embolization issue and all other questions.

DR. HURST: I think that's an important point that Sally brought up that we really need to focus on the intended use of these devices which is to occlude vessels. These are, in essence, vascular clamps. And that when we look at that vascular clamp does it close of the vessel safely and effectively and over the long term? And in fact, in many cases you can tell ten seconds later that, in fact, you've gotten complete occlusion of

the vessel by using a repeat angiogram. So that if we kind of focus on that issue, then we separate that a little bit from some of the long term clinical studies.

And I mention this because it's been a problem in the past because when we do many of these clinical studies we get wrapped up in the long-term clinical outcome of the diseases and it's very difficult to separate the overall disease from the intended use of the device. For example, somebody with arterio-venous malfunction in their thalamus is not going to be expected to do as well as somebody who has one in their right frontal pole, but nevertheless, they get lumped into the same group when we do clinical studies, simply because as was mentioned in the presentation, there are so few of these arterio-venous malformations. I not long ago looked at the experience of a very large institution here in this country for the deep central AVMs and over about a 10 year period they had seen 50 of these so that the statistical power that we're going to get from doing some of these clinical studies is maybe not as good as we might like. So I think focusing on the intended use,

that is, using this as a closure device is probably very important.

Secondly, I'm not sure that I would agree that we want to create two guidance documents, one for liquids and one for everything else. Because there's an overlap in here. Some of the devices we have had very long experience with, with detachable balloons, with PVA, we've had a long amount of experience, certainly 20 to 30 years. The same thing holds for the cyanoacrylate liquid embolic agents. There's a huge amount of experience with this. In contrast, some of the newer coils or particulate involved places that we might see come out may have novel detachment strategies or may, in fact, as Dr. Ku mentioned, have gene components or things like that that are very much differentiate them from devices that were on the market and available before. So it may be better for our guidance document to just address embolic devices in general rather than try and separate them out based on a liquid versus nonliquid status.

Let's see, I think those were the main things I wanted to mention.

CHAIRPERSON CANADY: Other comments from

Panelists?

DR. GATSONIS: I have a general question because I don't know very well myself the intended use of these devices and I agree with the formulation that they have to be evaluated, visibly, the intended use. But is the intended use always of a short term benefit? If there's any situation in which the device is going to be there in the long term and there will be long term benefit or harm to the individual, then I don't see how you could avoid doing -- how you could avoid the need for clinical studies and at that point the length of follow up as Dr. Ku suggested, should depend on the particular use.

DR. HURST: No, I agree. It has to depend on the particular use and in some cases you're going to need longer term follow up. As an example though, like I say, many of these devices are designed to occlude a vessel and stop blood flow and that particular aspect of it can be evaluated almost immediately.

In some cases, you're going to remove that at the time of surgery so it's not a long term issue. In other cases, you are going to leave it in there in which case it's a very big issue and

you do need to do longer term follow ups. Sometimes the material of which the device is made is one, for example, platinum, where we have a lot of data on what the long term effects of implanted platinum in the body are so that it may not be necessary to start a new long term study on this device made of platinum, for example.

DR. GATSONIS: I don't know if I agree with that in the sense that you may know what platinum is and how it acts generally, but you would not know what the specific device and the specific kinds of patients is doing in the long term. There could be a whole bunch of other items that you can not deduce from knowing how platinum devices in general have acted in the past.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: This is Sally. I actually think that maybe a best way to do that is to have, instead of having the guidance document say a clinical study with a one year follow up which in some years, sometimes may be too short and sometimes may be too long, is that we actually go back and say let's have the follow up, what's needed to prove the intended use of the device and its safety and efficacy for its intended use? And

if we leave it at that that lets the industry when they're coming forward with their protocols to the FDA, explain why a five minute follow up is sufficient versus a six month and it's them working with the Agency to figure out the best time of follow up for where they're headed.

CHAIRPERSON CANADY: Dr. Ku.

DR. KU: Yeah, I agree with that. The suggestion by industry to eliminate the part on presurgical consideration, I think, does open them to a completely different set of standards, because if you're going to do a brain AVM embolization with the material and that's going to be only therapy or a therapy in association with radiation, then you're talking about a significant follow up as compared to a presurgical treatment where they're going to take the lesion out the following week.

CHAIRPERSON CANADY: Any other general comments? If we could ask Lt. Commander Foy to put the questions up for us again and then we'll have the Panelists comment question by question if we could.

If we could start with you, Dr. Hurst, on question 1.

DR. HURST: Yes. I think that

certainly, once again, just to mention that I think that we need to emphasize the intended use. When we look at these different outcome scales, we can kind of divide them into acute neurological outcome and the long-term or outcome -- long-term outcome, rather.

Some of these -- for example, the NIH stroke scale -- are very good for determining acute neurological changes. Other ones, such as the Barthel Index and a modified Rankine, are much better for longer term outcome.

And, again, I think that if we get involved in doing a clinical study, the outcome scale appropriate to that clinical study should probably be done. If we're interested in looking at how often should patients have a stroke in association with the use of a particular device, then probably the NIH stroke scale is the appropriate one to use.

When you start getting into longer term ones, a Barthel Index or a modified Rankine might be a better thing. But, again, you have to consider that that may or may not be important in terms of measuring the usefulness or the intended use of the particular device.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: I think it's fortuitous that I'm following Dr. Hurst. All I can say is "ditto."

MS. WOJNER: Basically, I would concur that NIH stroke scale, Barthel, modified Rankines, are probably the most likely scales that should be selected. I guess my bigger concern would be the design with which they were being applied, because outside a repeated measure design with a patient serving as his or her own control, I think that the data would be relatively difficult to interpret, simply because of the heterogeneity of these vascular problems.

CHAIRPERSON CANADY: Dr. Ku, other comments?

DR. KU: No additional comments.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: I think the comment that we cannot apply a single scale, that they vary, needs to be reechoed. And that's all.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I agree with Dr. Walker, and I think that it should be up to the manufacturer to propose what is the best scale for the studies that

they're doing.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: No additional comments.

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: The question is very tough because, again, acute versus chronic, and acutely, in general, looking at what you've done to the patient with the embolization and the after effects, including swelling and other processes that can occur. I think it's very important to look at that.

If, on the other hand, you want to address the long-term effects, the long-term effects, again, can be measured with these basically acute scales or gross measurement scales of function. But you're really not addressing what you're doing to the person -- that is, the human aspect of the person -- with any of these scales in any significant level.

That is to say, really, the only scale -- if chronic measurement or chronically looking at what has happened to the individual, if it, in fact, is important to do that -- and I believe it is to a certain extent -- then actually neuropsychological testing is more important,

looking at the personality, the affect, the associations, the overall IQ.

But I don't think that that's necessarily the direction that we want to go because the intended use of the device is to block the vessels. And, again, the heterogeneity of the location is going to dictate, really, what you want to measure.

I think there needs to be some flexibility in the scales, and that as part of the scales inclusion of some form of neuropsychological testing, if it's important to that specific individual, or temporal lobe, or certain aspects of frontal lobe function are being affected.

Then, in that individual, in that specific case, inclusion of a form of neuropsychological testing, including Boston naming, frontal lobe function, IQ, may be very, very important. The Luria neuropsychological testing would be important.

But, again, I don't think that that is going to apply to a significant number of the patients that are getting the embolization, but it's going to apply to some and that's going to be far more important than looking at gross function

of whether the patient is hemiplegic or has ocular problems or other problems that these scales or level of consciousness, speech, etcetera, that these scales are measuring.

I think basically what I'm saying is included in this list, which could be applied to a smaller group of the patients getting embolization, we shouldn't forget that measurements of personality and what makes a person "human" should also be measured in a small percentage where it's applicable.

So, again, neuropsychological testing should be included on this, but not necessarily used in even a significant proportion but available. And it will become important in some of these patients.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: I don't have any further comments.

CHAIRPERSON CANADY: Any other general comments on question 1? We can move on to question 2. Dr. Hurst?

DR. HURST: Yes. I would say that what we need to do is we need to be using the imaging tools that are appropriate for what we are

interested in following. I think that at least in 1999, catheter angiography is really essential to determine whether the vessel is, in fact, blocked off, that you have an acute blockage of the vessel.

And, certainly, the status of MR angiography right now is not good enough to look at any sort of longer term follow up of vessel occlusion. That may or may not be necessary, depending on the length of follow up determined to be necessary for the particular device.

In terms of other imaging modalities, I think that MR is going to be essential if we're interested in looking at longer-term histological changes, edema, or whatever peri device changes might occur in the region of the embolization.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Yes. I think basically, insofar as tumors are concerned and MR, CT, is the imaging of choice, angiography for vascular disorders, I think basically that's all I would recommend, really.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: No further comment.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: No additional comments.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: No additional comment.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: No additional comments.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: I would just say that choice of imaging procedure, or whatever follow up, would depend on exactly how accurately you want to know outcomes. You may not always need the most accurate thing for a particular outcome, so there should be some leeway there.

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: No other comment.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: Just, once again, that if you're doing something pre-surgical, then the test will obviously be different than if you make a claim that the embolization or the closure of, say, an aneurysm is effective. Then you have to go out with angiography for a year or two.

CHAIRPERSON CANADY: Any other general comments regarding question 2? Question 3? Dr. Hurst?

DR. HURST: I think that blinding certainly does have a role in any sort of studies

looking at imaging data. In a particular case, it may or may not have a role. For example, many of these devices are radiopaque, and it's very difficult to be blinded when here's a film with a radiopaque coil on it, and here's one without one. You know exactly what happened.

So that I think that it's certainly a reasonable thing to include, but I'm not sure that it's always reasonable to require it.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Ditto.

CHAIRPERSON CANADY: Ms. Wojner?

DR. WALKER: No further comment.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: Same thing, except that the centralized reader may provide some benefit as it would reduce variability.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: No additional comment.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I agree with the comments made thus far, but I think we need to be careful not to add extra burdens that aren't necessary to prove the safety and efficacy of the device as it's being reevaluated.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: Yes. I don't think blinding is really very necessary in much of what this would be done in, and it's impractical in most of these situations. So I think it's very limited.

Having a central reader will -- for central readers with ways of dealing with disagreements will help in any kind of -- you know, help with the bias issue.

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: No other comment.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: I agree.

CHAIRPERSON CANADY: Any other general comments regarding that question? Number 4?

DR. HURST: I think that the use of clinical measurements -- for example, surgical time and blood loss -- it's certainly nice if you can find clinical end points that are very closely related to the intended use of occluding a vessel. Sometimes when we just look at surgical time and blood loss, and we try to compare various tumors, and we try to compare various AVMs, and we're really looking at apples and oranges. And it's very difficult to make those kind of comparisons.

And, again, I think if people have a fairly stereotype population of meningiomas, for example, some sort of a relatively common tumor, that's a nice thing to be able to do. But part of the problem in evaluating these embolic devices is that the individual pathologic processes are so, so different that they defy reasonable comparison in large numbers.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Yes. I think that there are just so many different variants of clinical presentation that it's very hard to reduce in a guidance document to cover all of those variants. So I think it would be difficult to specify those end points.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: I agree.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: For pre-surgical use, I think the industry's comment that an immediate pre- and post-angiogram is sufficient is probably a very reasonable one. The reason is that your end point is going to be very, very short in time course, and the post-embolization angiogram is going to be fairly reliable in determining the percentage of

occlusion.

Now, for tumors, obviously, a post-embolization angiogram and a post-embolization CT or MR will provide information as far as percentage of occlusion of the tumor when compared to the pre-embolization studies.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: I think Dr. Hurst and Dr. Ku have made the points that need to be made.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: No further comments.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: No other comment.

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: No other comment.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: I agree this is ridiculous.

(Laughter.)

CHAIRPERSON CANADY: Spoken like a true neurosurgeon.

Any general comments about this question? Number 5?

DR. HURST: I think that collateral vessel formation -- this can be kind of tough. I think that if you're talking about a permanent

device, a permanent occlusion, at least in 1999, if you want to look at it long term you have to do catheter angiography. And in many cases, that really is not going to make the differentiation.

If you have a clear-cut case of a vessel absolutely reopening, in many cases that's fine. If you have collateral vessels that have reformed around that in an arteriovenous malformation, for example, that could be difficult to differentiate. And that's a normal process that will occur in these lesions.

So it's a tough thing, but I think in 1999, if it's necessary to look at that, an angiogram is going to be the way that we've got to recommend to do that.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Yes. I think that -- I'm even wondering if item 5 needs to be included in the guidance document as such.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: No further comment.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: I agree with Dr. Hurst. For collateral formation, if you have what you think is a successful occlusion, looking for early

collaterals is very reasonable at three to six months. But you definitely need a long-term follow up, like in two years, to demonstrate that you have permanent occlusion of your lesion.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: No further comment.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: No further comment.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: No further --

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: No other comment.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: If the claim is being made that an arteriovenous malformation is being cured or completely closed down, then there has to be appropriate basis for that by angiography to show that the embolization has closed off the nidus correctly and that collateral can't develop. So it is an important question to answer.

I don't think the companies will make that claim because it's going to be very difficult to prove long range. So as long as the claim isn't being made, then I think just early angiography may be enough to substantiate a single claim that at

least blood vessels are closed.

CHAIRPERSON CANADY: Any general comments on question 5? Dr. Edmondson?

DR. EDMONDSON: No. Just the reiteration, given what Dr. Penn said, that really perhaps we should indeed delete item 5 because post-angiography should indicate that the job is done, and clinical follow up is separate and apart from the burden of industry to demonstrate that this is safe and effective.

CHAIRPERSON CANADY: Any other comments? Ms. Witten?

DR. WITTEN: No, I just want to make a comment before you answer question 6.

CHAIRPERSON CANADY: Okay. Go ahead, then.

DR. WITTEN: Okay. Do you want to -- you're finished with question 5?

CHAIRPERSON CANADY: Yes, we have.

DR. WITTEN: Okay. When you're going around to answering this, I just want to make a comment that we're interested in what you have to say with respect to evaluation of the patients, not just for effectiveness in terms of the embolization but any safety end points that you think need to be

captured at one year or at some other time point with another imaging method, or a physical exam.

So 6 should not be looked at just in terms of the embolization effectiveness, but the safety of the procedure also.

CHAIRPERSON CANADY: Thank you.

Dr. Hurst?

DR. HURST: I think that that's a very important point to make. That the follow up is really going to be determined by exactly what's left in that person, and how much we know about that particular material or device already.

I think, again, in the case of many of these agents, PVA, the material -- the platinum material with which the coils that are already available and have been available are made, the cyanoacrylates, we know a great deal about what they do over the long haul. And doing long-term follow up studies on people who have those left in place is probably not really a reasonable thing to do.

When we start talking about new materials with which we have no significant experience, then I think that there certainly needs to be long-term follow up. And a year may be a

good ballpark, but that may not even be enough if we're talking about, for example, a gene product left on an implanted device.

So I think that it has to be based on the type of material that's left in place, in the case of things we know about, not very long at all, if any; in the case of new materials about which we have little or no knowledge, perhaps very long.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Yes. Basically, if most of the materials, singly or in combination, have already existed for several years, and there is a body of experience over a time course of 30 years, let's say, then, in fact, for these existing materials we should eliminate the one-year follow up requirements and really specify in a shorter order aims such as for, in fact, aneurysms.

And perhaps a post-angio is really sufficient and maybe a three- or six-month follow up requirement in that instance. For tumors and the like, a more extended follow up.

But basically, I think that should be well foreshortened for existing material, and for new material, again, it should be stratified according to the clinical circumstance.

CHAIRPERSON CANADY: Ms. Wojner?

DR. EDMONDSON: But should be at least a year.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: No further comment.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: I think it's important to reiterate the difference between the effects of the device and the disease or disease progression, and that the follow ups for the two should be done differently. So it needs to be done on an item-by-item basis.

For devices that are bio-active or genetically active, obviously you'll need a much longer term follow up. For devices that are made out of materials that have been in use for a number of years and their properties are well studied, the follow up probably does not need to be very long.

For devices that are variations of existing materials, new types of cyanoacrylates or new types of particulate embolic materials, then you have to tailor it according to that material and how well that has been studied or not been studied.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: Dr. Ku did a good job of differentiating between old materials and new materials. I'd like to add that I'm a little uncomfortable with the FDA specifying particular imaging modalities in their guidance documents, and perhaps leaving that best up to the discussion between the FDA and industry for what modalities are most appropriate for each device in order to determine long-term effectiveness.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I'm going to agree with both Dr. Ku and Dr. Walker. And I think we need to make the guidance document general enough so that people don't get forced into a bucket. And I would propose that we -- if there's going to be clinical trials, we leave it up to the manufacturer, working with FDA, based on their device to come up with the appropriate follow up time.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: I would just reiterate the distinction between -- a conceptual distinction between a particular type of material and the use of that material for a particular disease or for a particular condition. Even if there is a lot known about the material, I don't see how putting it to a

particular use obviates the need for looking at its long-term effects.

So I would be very reluctant to accept notions that we could use this without a real follow up, except if there are situations in which the intended use is really for the next 10 minutes or just up to the surgery, and so on.

Any device that makes -- that is going to be left in the patient and makes -- in a sense, it makes the implicit claims to long-term effectiveness should be evaluated with the follow up that is commensurate with whatever the claim is.

CHAIRPERSON CANADY: Dr. Gonzales?

DR. GONZALES: When you're looking at the risk-rewards in a clinical trial, I think that it's important to also look at the treatments that are now limited by -- or due to the embolization. That is to say, for instance, tpa may not be given to a stroke patient where the stroke is unrelated to the AVM that has been embolized.

And right now, the guidelines for that, I believe, are three months. That is to say, once a patient has had any neurosurgical procedure on the head, or embolization to vessels in the head, you can't give tpa, or, for that matter, the risks

are higher also for anticoagulants, so that, you know, that will help in terms of setting up the time period.

Certainly, three months, I believe, is the time period for post-neurosurgical embolization procedures that you can give tpa. This is going to be a factor, I think, in, again, measuring the risk-rewards when you're doing these clinical trials. I mean, after all, that's what you're trying to do is see what -- ultimately that the embolization is not only short term but long term having its proposed effects.

So I would say that the clinical trials that are being proposed here should also measure, and that is to say the sheet or the information that has to be filled out by the individuals that are doing the embolization should also somehow include in the follow up of these patients what happens to these patients over a short period of time of at least three months, possibly a year.

But also to include the fact that patients are restricted from treatments, not just what happens to them physically from the embolization or compromise that they have from the embolization, but things that can no longer be done

or given to improve that patient's status from unrelated problems, but now you're restricted because of the fact that embolization took place.

So I would ask that under these clinical trials that we make sure that we include treatments that are now limited due to the embolization.

CHAIRPERSON CANADY: Dr. Penn?

DR. PENN: I'd just make a comment about a special category of studies, and that would be the aneurysm studies. We have to compare aneurysm eventually being fixed intravascularly with being clipped. And that means we have to have very good data, certainly at a year angiographically, to make sure that the aneurysm still has been excluded from the circulation.

And in those particular studies, the FDA should take special care in making sure that the claims that are going to be made can be tested. And I would think that with the treatment of aneurysms the FDA should be very stringent about that.

DR. HURST: Could I make one other comment?

CHAIRPERSON CANADY: Dr. Hurst?

DR. HURST: I would really agree with

that. We mentioned that for AVMs the claim probably will not be made of complete closure of the AVM, and that's fine. But, again, for these aneurysm cases, this is a new modality, and follow up of these patients is going to be very, very important.

CHAIRPERSON CANADY: Any other general comments on question 6? Any other questions you are left with, Lieutenant Commander Foy?

LIEUTENANT COMMANDER FOY: I would like to remind you that it was commented that the indications for these devices are not limited to pre-surgical.

DR. PENN: Can I just make one comment? Having done -- a long time ago -- some of these studies on animals, I don't think that animal studies should be considered the sole basis of using these materials, and that human clinical studies are mandatory.

And to imply that you have enough information from an animal study to know whether you can occlude a vessel permanently, or use it effectively in a human situation, is not something we want to write into the guidance.

CHAIRPERSON CANADY: Other comments?

We're going to adjourn for lunch. I'd like you to come back and be ready to start at 12:30. Your lunch will be here at 11:30, so take a few minutes to gather your thoughts. But we're going to try to start promptly at 12:30 because people have transportation issues.

(Whereupon, the proceedings went off the record 11:21 a.m. and resumed at 12:30 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:31 p.m.)

CHAIRPERSON CANADY: I'd like to call the meeting back to order. This is Neurological Device Panel. We're going to be discussing this afternoon the reclassification petition for the totally implanted spinal cord stimulator.

The form the afternoon will take is we'll have a period of open comment, we'll have an FDA presentation, we'll have a presentation by the petitioner, a presentation by another industry representative, and then comments from Dr. Edmondson, from our panel, and have open discussion.

At this time, I'd like to invite any open public hearing, any public people who would like to speak regarding this issue. If none, then I'd like to introduce Dr. Kristen Bowsher, who will discuss the FDA's presentation.

DR. BOWSHER: Hi. I'm Kristen Bowsher, and I'm the lead reviewer for the reclassification petition for totally implanted spinal cord stimulators, the petitioner's advanced neuromodulation systems, or ANS.

I'd like to start by giving a brief

description of the device itself. The device -- the main components are an electrode, either percutaneous or paddle, that are implanted along the spinal cord. The electrodes are connected to electrode leads, which for the totally implanted stimulators, which we're talking about today, the leads connect to a pulse generator that is actually implanted into the patient.

Now, the Class II devices use an external pulse generator that uses radio frequency to send signals to the receiver that is implanted into the body.

The intended use of the device is the treatment of chronic intractable pain of the trunk and limbs. There are currently two PMA-approved totally implanted spinal cord stimulations -- Cordis Corporation, on April 14, 1981, and Medtronic Incorporation on November 30, 1984. The petition was received from ANS by the FDA on June 16, 1999, and it's proposing reclassification from Class III to Class II.

Now, although we are discussing Class III totally implanted spinal cord stimulators today, I'd like to quickly review some of the regulatory history of the similar Class II radio

frequency coupled devices that I've described frequently previously.

Back in 1978, a classification panel recommended Class II, and they identified these risks to health that they believed could be controlled by special controls. On November 28, 1978, FDA concurred in an FR Notice, and the RF coupled spinal cord stimulators have since been Class II, 510(k) devices.

With that as background, I'd like to now discuss the risks associated with the totally implanted spinal cord stimulators that are the topic of today's discussion. These are the MDR reports as reported in the petition from ANS. They represent only totally implanted spinal cord stimulators or the Class III devices, and were collected from the FDA web site and MAUDE and cover from 1984 to March 22, 1999, excluding 1991 because there is a problem downloading that information.

When looking at these, I want to stress that while these reports allow us to get a feel for the types of risks, they cannot be used to calculate rates of actual events.

This is a list of the risks to health that FDA has identified from information available

to us, including MDR reports and literature. Note that these risks were all identified by ANS in their petition, with the exception of battery leakage.

The petitioner has proposed a special controls guidance document, standards, and labeling.

Now, I'd like to ask the panel to keep in mind the following four questions that were included in your panel packet during your discussions. Near the end of your deliberation, we will be asking you to specifically address them prior to classification recommendation.

The first question deals with risk identification in the patient population. The second question deals with the special controls. The third question deals with the classification itself. And the fourth question deals with the indications.

Thanks.

CHAIRPERSON CANADY: Any questions for Dr. Bowsher?

Then at this time, if we could have Mr. Drew Johnson, who is the Director of Regulatory Affairs for Advanced Neurological Systems.

DR. JOHNSON: Good afternoon.

CHAIRPERSON CANADY: Good afternoon.

DR. JOHNSON: I took my coat off because I feel a little bit more comfortable without a coat on.

My name is Drew Johnson. I'm Director of Regulatory Affairs for Advanced Neuromodulation Systems, Inc. And the agenda for our presentation today is as follows. I'm going to give a brief introduction to the presentation, followed by a basis for the reclassification.

Then, our next presenter will be Dr. GianCarlo Barolat, and he will review the device similarities and differences, as well as a summary review of the literature and risks and indications that were submitted within the petition.

And then, Dr. Tracy Cameron will give us a summary of the MDR reports, and I'll come back and go through the proposed special controls, followed by a closing statement.

Before I get into the risk and benefits -- excuse me, before I get into the basis for reclassification, I'd like to just review some of the regulatory historical events that are associated with spinal cord stimulation. As

Kristen said earlier, in 1978, a panel recommended that the Class II device -- that the implanted spinal cord stimulator device be classified in the Class II. In 1979, it was formally classified.

In 1980, a manufacturer submitted a 510(k) pre-market notification to the FDA for clearance of their internally powered spinal cord stimulation device as a Class II device, and tried to prove substantial equivalence to an external spinal cord stimulator device that was externally powered.

The FDA at that time deemed that the PMA -- that a PMA was necessary. This particular manufacturer at that time had the opportunity to go through the reclassification process and did not.

In 1981, the first implantable power generator for a spinal cord stimulator was approved through the PMA process.

There have been quite a few changes in law since 1984 -- 1981, and those particular changes in law really are relevant to what we're trying to do here today. There was the change -- an amendment to the Food, Drug, and Cosmetic Act in 1976, and this modification facilitated the FDA and industry having more flexibility to provide

reasonable assurance of safety and effectiveness for devices.

In 1990, with the Safe Medical Device Act of 1990, it has instituted procedures for establishing performance standards. It required manufacturers' compliance with design controls, and, most importantly, it changed the definition of Class II devices to include the use of special controls as a means of providing reasonable assurance of safety and effectiveness.

And then, as recent as 1997, with the passage of the Food and Drug Administration Modernization Act, there were two key elements of this particular Act. One, post-market controls could be applied to the classification of devices to provide reasonable assurance of safety and effectiveness; and, two, the use of international standards.

The FDA is authorized to recognize standards and require declaration of conformance as part of the 510(k) clearance process.

Now, it brings us to where we are today. And through our literature review, and through our applications of special controls assigned to the risk found in our literature review, and the MDRs

that we reviewed, we believe that we have a basis for reclassification of this particular device.

We believe that the risk and indications are similar to a Class II implanted spinal cord stimulator. We believe that general controls and special controls are available to reasonably assure the device's safety and effectiveness.

And last but not least, if you look at the literature -- and as shaky as MDR data is -- over the past 10 years, the use of this device certainly demonstrates that it is safe and effective for the treatment of chronic pain of the trunk and limbs.

Now I'd like to bring up Dr. GianCarlo Barolat to discuss the similarities and differences, as well as the literature, the risk, and indications.

Dr. Barolat is a neurosurgeon. He is the Director of Neurological Services at Thomas Jefferson University. He is President of the International Neuromodulation Society. He is co-editor of The Journal of Neuromodulation. He has published over 60 articles in peer review journals. And it should be noted that Dr. Barolat has implanted both types of these devices for over 15

years.

There's one more thing I'd like to say, that our reclassification petition is not to reclassify this device outside the current classification for RF systems, which is spinal cord stimulation for the indication of the treatment of chronic pain of the trunk and limb -- trunk and/or limbs, either as a sole mitigation agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. And, again, this is the same indication as the current Class II device.

And now I'd like to bring up Dr. Barolat.

DR. BAROLAT: Thank you.

Good morning. I'm GianCarlo Barolat. I'm Professor of Neurosurgery at Thomas Jefferson University in Philadelphia, and I have been implanting these products for about 20 years. And I have had a lot of experience with basically all of the products that have been on the market, and I have a consultantship agreement with ANS, as well as with Medtronic.

Now, just to give you a little overview here, what are the components of a spinal cord stimulation system? Let's start from here. The

electrodes that are implanted in the spine -- without the electrodes in the spine, we would not have spinal cord stimulation.

Then you have the case, which is implanted in the body. Then you have the power sources, which can be inside or outside of the body. And then you have the circuitry. And as we'll see in the next slide, there are two types of circuitry. And then you have the programmers, which is what is given to the patient to control the device.

Now, some parts are outside of the body, and some parts are inside of the body. And as we look at the two types of systems -- the radio frequency system and the implantable pulse generator -- we see that there are some differences.

These are the parts that are outside of the body. In the RF system, outside of the body you have the programmer, which also activates the internal part; then you have the power source, the batteries, which are either rechargeable batteries or regular alkaline batteries; and then you have the stimulation control circuitry, which generates the signals that activate the other unit.

Inside of the body you have the case, and you have the decoding circuitry that receives the signal from here and sends it to the electrode. And, of course, the electrode is inside of the body.

In the full implantable system, outside you only have the programmer, which is what the patient is given. Inside of the body you have the case, you have the stimulation control circuitry, and then you have the power source, which is a lithium battery. And then, of course, you have the electrodes.

And these are the programmers that are currently on the market that are given to the patient. This is the ANS programmer, which the patient has to wear in order to activate the system. And this is the Medtronic programmer, which is only used to change the parameters and turn the device on and off. After that, the patient does not need to wear that.

Besides that, the physicians are also given a different programmer, which is a more sophisticated one, which allows to change settings that are not allowed to change for the patient.

Now, spinal cord stimulation has been

used since the late '60s. I've been involved with implanting these devices in the mid '70s. I would say that the current IPG and radio frequency systems have been in use for well over 10 years for the treatment of chronic pain.

And if you look at the literature across the board, the success rate for spinal cord stimulation in the treatment of chronic pain is about 50 to 60 percent. And, really, for practical purposes, when it comes down to patient's care, the main difference between the implantable systems and the radio frequency devices is the power source being on the outside for one and being on the inside for the other, and the patient having to wear the external device for the radio frequency system.

Now, we did a literature search to look at complications, look at the complications of spinal cord stimulation, and we found 31 articles since 1983 in English that listed the complications. And we grouped the results according to the type of complications.

And it should be clear that from the literature it was not specified whether the systems were radio frequency or full implantable pulse

generators. But some of the complications are clearly related just to the electrodes and have nothing to do with the pulse generator. Lead migration, epidural hemorrhage, with or without paralysis, leakage of cerebral spinal fluid, these have nothing to do with the pulse generator.

And then, infection, which in my experience is almost always at the pulse generator site, undesirable changes in the stimulation over time -- as you can see, that's a very small percentage -- pain at the implant site, allergic reactions or rejection, very rare in my experience, local skin erosion over the receiver, device failure, which could be either breakage of the leads or the cables or failure of the electronic components.

And these are the complications that are in common with both types of devices. And my experience is that the most common complications are related to the lead migration and/or infection.

And then complications that are exclusive to the implantable pulse generator -- from the literature search, battery failure, which, of course, you don't have with the radio frequency system because you use external batteries, and that

was 1.8 percent.

Now, if I look in my practice -- this is what's in the literature -- if I look in my practice, I have implanted maybe 1,500 of these systems since 1985, and there is two additional complications that I have had that are exclusive to the IPGs. And one is leak of the acid in the battery, which occurred in a device that actually never went to market and has not been implanted since maybe eight or nine years. And I had a few instances of that, just with that one device.

And then I have had occasional patients who have received jolts, power surges, when they go through metal detectors or those theft deterrent devices in the supermarkets.

I would say that in my experience the infection rate, the pain at the sites, is about the same for both the radio frequency and the pulse generator.

What are the indications for spinal cord stimulation? I would say that the indications are shared between the two types of systems. Chronic pain makes up for the bulk of it, and the different subcategories of chronic pain -- RSD, causalgia -- they are part of the complex regional pain

syndromes.

And then different pains -- neuropathy, brachioplexis, nerve root avulsion, failed back surgery -- as you know, that probably makes up for more than half of the implants today in the United States -- neuralgias, arachnoiditis, and then pain due to peripheral vascular disease, and pain due to angina, which are two relatively more recent applications.

What are the contraindications to the procedure? Well, we usually do a trial before we do the implant. And, obviously, if the patient does not obtain pain relief, that's a contraindication to the implant. A second contraindication is if the patient cannot understand -- comprehend how you operate the device, then unless you have somebody else that can do it for him, then I would not implant somebody.

And then there is limitations in patients who have cardiac pacemakers, and certainly patients who have to have MRIs should not have the implants.

What are the benefits of having the total implantable system versus the radio frequency system? Well, there are several advantages, as you

can imagine. There is no external hardware that should be worn all the time. So it's more appealing cosmetically. There is no restrictions to what you can wear. You can go in the water and still have the benefit of the stimulation, where with the radio frequency system, if you go in the water, you have to remove the antenna and so you cannot have the stimulation.

And then you don't have to use the antenna, and that's a major factor because if you're perspiring, for instance, then the antenna will not stick to the skin. And so you cannot use it.

And also, you don't have to go through the trouble of making sure that the antenna is aligned with the device in the body, and if he moves just a little bit then you might lose a stimulation, or it might be too strong. So there are definite advantages to having a totally implantable device.

So in my opinion, when I look at all of the pros and cons, I would say that, first of all, both the radio frequency devices and the totally implantable devices share the same indications. And for practical purposes, when I discuss this

with the patient, the main difference, at least for the patient, is the fact that the power source is on the outside instead of being on the inside.

Also, when I review my complications, outside of those specific ones that I mentioned that are related to the internal battery, the other complications are basically very similar for the two types of systems. And the other very important consideration is that having the inside battery -- sure, it carries a little bit of a risk, but it's less than the risk of having to do repeat surgeries to replace it. That risk is well worthwhile.

And that's the end of my presentation.

MS. CAMERON: Hi. My name is Tracy Cameron. I am a Senior Scientist with ANS, and I'm going to report on the MDR search that we did.

Before I start talking about the specifics to our search, I'm going to talk a little bit about MDRs. First of all, MDRs are incident reports, and these alleged incidents are placed into categories at the time of entry, before any analysis has been done.

The categories that are used are death, serious injury, and malfunction, and usually these are placed into these categories by the

manufacturer themselves.

In order to do -- because these events are alleged incidents, in order to do a proper analysis of the database you are required to actually review each individual report and assess what actually happened in those cases. If you don't do that, it can lead to a high level of false positives when you're looking at these MDRs.

And I have an example of one that -- I hope you can see it, but I think you have -- you might have it in your handouts. This is an example of an MDR that was pulled up looking at spinal cord stimulation. Now, this MDR could be placed in the category of an IPG. However, upon further investigation, we found that this is actually an RF system. So it would be misrepresenting to put it in with IPGs.

Also, if you look, it's been reported as a death, which means -- which would imply that the device had something to do with the death of the patient. However, when you read the description, you see that it says there was -- that they did not feel that there was enough information to suggest that the product actually contributed to the death of this patient.

So using this MDR without reviewing it in detail may cause people to think that an IPG would have caused the death in this situation. And actually, like I said, this isn't even an IPG.

Now, I'm just going to go over how we did our MDR search. We used MDR and MAUDE searches, and we performed a search using manufacturers' names and the term "neuro." This gave us a total of 1,386 reports from the time 1984 to 1999. We started with 1984 because this is when the most -- the currently available IPG system came on the market.

This search was further refined by identifying those reports which only talked about IPG systems. So we excluded all RF systems from our search. And also, we only included those IPG systems which are currently in commercial distribution because they have had the longest duration, the longest time out in the market.

We found a total of 408 reports when we did this, and we categorized them according to adverse events, and we used the same risks that were found in the literature review. This allowed us to compare the two types of searches.

However, there was a problem when

looking at the MDRs, and that is that often there is not enough information in the MDRs to place it in a category. They just don't have enough information in them to determine what you -- put it where you want to put it or where it should go.

And I'm going to show you an example of one that we found, and what we did with them was we placed them in an "other" category because we just couldn't say anything. And this one, it says that the device -- that it was explanted because of a possible failure. So we couldn't determine where that should go.

Now, the results of our search were we had the largest category in "other" -- 144. The second largest was related to undesirable changes in stimulation over time. The third was related to battery failure. However, they were all pre-end of life battery failure in our search. The fourth category was device failure, and this included -- we included lead breakages, hardware malfunctions, and loose connection in this category.

Fourteen reports were related to infection, 10 to pain, two to skin erosion, and we had one lead migration, one seroma, and one allergic reaction.

Basically, from our MDR search, we did not find any new risks that hadn't already been identified in the literature search.

Before I finish, I just want to say that there were limitations to our MDR reporting. And the first one is that we obviously couldn't include events that went unreported. Also, the other limitation was that there were a number of incomplete reports, which we had to group in the "other" category. There was not enough information.

Third, we don't know what the total number of devices that were implanted over these years were, so we have no denominator for the numbers.

And, finally, as was mentioned earlier, the MDRs for 1991 were unavailable due to a problem with the MDR database.

Now I'm going to introduce Drew again. He's going to talk about special controls.

DR. JOHNSON: Again, Drew Johnson, Director of Regulatory Affairs for ANS. How are we doing on time, Madam Chair?

CHAIRPERSON CANADY: You've got about seven or eight minutes.

DR. JOHNSON: Okay. I'll try to run through this.

Just to refresh everyone's memory about Class II devices and how are they defined, because it's paramount to what we're trying to do here today. And as I said earlier, the Safe Medical Device Act of 1990 really changed the definition of the Class II device to be what you see there, and that is a Class II -- the devices in Class II, the general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness.

And there is sufficient information to establish special controls, including the promulgation of performance standards, post-market surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance.

ANS has identified several risks from the literature. And using the information as we best possibly could from the MDR data, and from these risks, we have assigned special controls. I'm not going to go through each one.

The point here is that for the risk that

we found, we were able to find a multitude -- a multitude of special controls, not one for each risk but a multitude.

And Tracy and Dr. Barolat went through the risks in the literature, so I'm not going to bother you with going back through that. But these are the same risks that were listed in the petition.

I'd like to talk a little bit about the risk of battery failure, and how that relates to the petition and our device. Of course, there is an internal battery within the totally implanted spinal cord stimulator, and we don't want to make light of that or pretend that that's a simple issue.

However, since the laws have changed over the years, we believe that there are standards available that cover both implanted and explanted devices. As a matter of fact, the ANSI standard, the participants from the opposition, had an opportunity to participate within the development of that standard, and also other industry representatives and users in the field.

A year or so ago, there was an international standard that was harmonized. It's

called the Active Implantable Medical Device Standard. It's EN 45502. That particular standard is available. And by the way, that standard is accepted for use on not only a device like a spinal cord stimulator but for other devices that are more life-threatening.

And you say, "Well, that's all well and good. But what about the standards that we use here in the United States and the controls for that?"

DR. GONZALES: Excuse me. I'm sorry.

DR. JOHNSON: Yes.

DR. GONZALES: You said the standard for implanted and explanted. Do you mean implanted and external?

DR. JOHNSON: External. I'm sorry.

DR. GONZALES: Okay.

DR. JOHNSON: I'm sorry. Implanted and external. I'm trying to meet Madam --

CHAIRPERSON CANADY: You're doing okay.

DR. JOHNSON: -- Chairman's time here.

(Laughter.)

CHAIRPERSON CANADY: It's not that strict.

DR. JOHNSON: Okay. All right.

CHAIRPERSON CANADY: You are the petitioner.

DR. JOHNSON: All right. Thank you. Thank you, Madam.

Other controls that are available for this type of device are specific labeling controls, which would include warnings, precautions, and adverse events within the labeling. I might add that these warnings, precautions, and adverse events that we are proposing here are the same ones that are available now for the Class II device, the same ones that are available for the Class III device.

I'm not going to go through each one, but the FDA can make the determination as to what specific labeling should be required as that control.

And last, on the labeling slide here, is the standard prescription statement.

And here are some labeling controls that are unique to the internal battery. We believe that manufacturers shall provide a chart or calculation in the physician's manual which would illustrate the range of estimated service life of the device for various output selections.

We believe that manufacturers should have a low battery indicator on the patient programmer-user interface. We believe that manufacturers should have an end of battery life indicator on patient programmer interfaces.

Let's talk a little bit about internal battery. People who are not used to design processes may say, "Well, you're trying to put a battery on someone. How are you going to control that and make sure the manufacturers out there can adequately control that and make sure that it is safe?"

Well, because of some of the laws that we talked about, there are now things in place that allow manufacturers to do that. Design controls were initiated. There are standards, like risk assessment standards, the EN 1441 harmonized standard.

There are safety standards, like the EN 45502. And then sometimes manufacturers have to go to other standards based on risk assessment and specifications, based on their risk assessment of devices. And then, again, there is labeling.

Now, if a manufacturer is making a device -- say, the implanted spinal cord stimulator

with a battery in it -- and he thinks that the battery is a risk because it's implanted, that manufacturer would use a risk assessment which is based on the EN standard and a recognized standard that the FDA recognizes.

And this is some of the ways that a manufacturer out there in our world would go about determining how they are going to identify what those issues might be, what are the risks to those issues, what kind of controls can they use to mitigate those issues. This is how it works, and this is how we can use the EN standard for risk assessment and other specific standards.

As I said before, there is a standard that was established and reestablished, really, back in 1995, and this standard established safety and performance requirements for internally and/or externally powered spinal cord stimulators. There's the recently approved and harmonized EN standard that I talked about a little bit earlier.

And then there's the standard that's a risk assessment standard, and I'd just like to spend a few moments talking about the bullet points that I have here and how this relates to what I

discussed in the previous slide on risk assessment.

This particular standard specifies the procedure for the manufacturer to investigate, using available information, the safety of medical devices, including in vitro diagnostic devices and/or accessories. It's used to identify hazards, estimate the risks associated with that device. It also is used to assist in areas where relevant standards are not applicable or not used.

This is how a manufacturer goes through the process that I talked about earlier, identifies the risk, identifies the hazards, the risk associated with it, and then the manufacturers -- it's on the onus of the manufacturer -- to go in and define what kind of special controls are controls in the manufacturing process, or standards or specifications that he can use to mitigate that risk.

And by the way, FDA requires, through pre-market notification, and in some PMAs, that this information is provided.

Other controls are guidance documents. And, again, we're not talking about one or two guidance documents that can control these particular risks. We're talking about several.

Most importantly, I think because of the importance of the implanted device, the high technology of the implanted device, there are guidance documents that can handle that, along with special controls such as standards.

Again, we're here today to ask the panel to consider reclassifying this device to a Class II. We believe that the risk and indications are similar to Class II implanted spinal cord stimulators. We believe that there are general controls, an abundant amount of special controls that are available to reasonably assure the device's safety and effectiveness.

We also believe that we've shown -- and if you read it yourself, you will see that over 10 years of use demonstrates that this device is safe and effective for the treatment of chronic pain of the trunk and limb. And it's important here that we're not trying to get into angina, we're not trying to get into sacral nerve root stimulation. We're talking about the same indication, that this device has been used for over a number of years.

And last, I'd like to say that I believe that reclassification of this device is good for the FDA. I think long term it may spur

competition, which may drive prices down, which would be good for the consumer.

And last, but not least, I believe that the special controls that are not in place today, not 1981, not 1991, we're talking about today, that these special controls will not allow devices to be put into the market that will cause any more harm or risk to patients than the current Class II device.

Thank you.

CHAIRPERSON CANADY: Thank you very much, Mr. Johnson.

Any of the panelists have any questions for any of the ANS speakers? Dr. Hurst?

DR. HURST: Yes. Can you tell me the battery life of these implanted stimulators?

DR. JOHNSON: I'd like to bring up our research development -- this is John Erikson, our Vice President of Research and Development.

MR. ERIKSON: John Erikson, ANS. It depends on the battery capacity that's in the cell that you put in the device. So it's by design, how big a battery you have. I'm not sure --

DR. HURST: I mean, what are we talking about, a couple of years?

MR. ERIKSON: It depends on the parameters. It could be two to five years. Could be less if you turn the -- all of the parameters wide open.

DR. HURST: I see. And how does that compare with the ones that are currently available?

MR. ERIKSON: Are you talking about our device or --

DR. HURST: You don't have any currently available, I don't --

MR. ERIKSON: We don't have one currently available, correct.

DR. HURST: The ones that are on the market now, how does that --

MR. ERIKSON: It would be equivalent or --

DR. HURST: -- with the battery --

MR. ERIKSON: -- bigger battery than what's currently on the market.

DR. HURST: It's a bigger battery?

MR. ERIKSON: Yes.

DR. HURST: How much bigger?

MR. ERIKSON: We currently have a --

DR. HURST: I'm just trying to get a feel for how long the battery --

MR. ERIKSON: About 30 percent bigger.

DR. HURST: Okay. So that would be, what, a one- to four-year battery is available now, and this would be a two- to five-year -- I'm not trying to hold you to the numbers. I'm just trying to get a feel for how often --

MR. ERIKSON: If you use equivalent settings, correct.

DR. HURST: I see. Okay.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: As long as you're up there, let me ask you another question.

MR. ERIKSON: Okay.

DR. WALKER: There is another type of implanted pulse generator that's used for the treatment of radiocardium, more commonly known as a cardiac pacemaker. From a manufacturing/engineering/ quality control point of view, from what goes inside -- because they both look the same -- what's the difference between a spinal cord stimulator and a cardiac pacemaker, other than different rates, different outputs?

DR. ERIKSON: I have the experience, but Medtronic would probably be better to answer that. But I'll try and answer that.

I believe they would be the same. At least what we're designing and building will be the same identical controls in place as the cardiac pacemaker. The EN standard is used for cardiac pacemakers, and we would be -- we're using that standard for our development.

DR. WALKER: As a follow up, are cardiac pacemakers Class II or Class III devices?

MR. ERIKSON: Cardiac pacemakers are Class III devices. They are a life-sustaining product.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I'd just like to take this opportunity to remind the panel that we're not looking at any particular device but a classification of device. So while it might be important to look at what type of battery lives we're talking about, it's not important specifics.

DR. GATSONIS: One item that was brought up is the risk of additional surgeries because the RF device fails versus the risk of battery failures in an IPG. Do you have any data that quantifies this?

DR. JOHNSON: Could you repeat that question?

DR. GATSONIS: Do you have any data on --

DR. JOHNSON: The whole question. Excuse me. I'm sorry.

DR. GATSONIS: Yes. What I wanted to say is that one of the key -- one of the items that seemed key to me in making the comparison between IPGs and RFs -- or FRs or whatever it -- is the risk of additional surgeries that will happen because, say, an RF fails versus the risk of, say, a battery failure in an IPG.

In other words, what is it ultimately that you gain by the IPG? And what extra risks do you generate? It seems to me that that is sort of one of the salient questions in terms of answering the issue of reclassifying this.

DR. JOHNSON: Okay.

DR. GATSONIS: Do you have any data, any numbers, about this?

DR. JOHNSON: I'll let Dr. Barolat answer the question, but I'd like to clarify your question. I think you meant that, what's the difference between the IPG, which has the battery and the shorter life span -- the external device, the battery is on the outside, so you just change

the battery on the outside. The internal device has the batteries --

DR. GATSONIS: Yes, I understand.

DR. JOHNSON: -- on the inside, so you --

DR. GATSONIS: I understand. I noticed in Dr. Barolat's presentation you were mentioning the risk of extra surgeries needed for RF devices. Do you have any quantitative data on this?

DR. BAROLAT: Well, the risk of replacing the battery -- with internal pulse generator, it's a guarantee with the currently available systems that you will have to replace the battery. So you guarantee that every X number of years you have to have an operation.

With the radio frequency system, you don't. Unless the system fails, you never have to have another operation.

DR. GATSONIS: Okay.

DR. BAROLAT: The risks of replacing the battery, of the surgeries that you would do repetitively, in my experience are minimal. Really, the main risk is infection because there is no risk of damage to the nervous system because you're just operating under the skin.

So the main risk is infection, and I would say my experience -- the infection, by changing the batteries, is maybe two percent, let's say. So it's a very small risk.

DR. GATSONIS: Okay.

DR. BAROLAT: And you have to pitch that against the advantage of being able to use the stimulator more effectively for the patient.

DR. GATSONIS: Okay. Then I misunderstood, because I thought I understood you to say that the IPG has less of a risk -- I mean, saves in repeated surgeries down the line. I misunderstood you.

DR. BAROLAT: No, no, no, no. With the IPG, you're guaranteed --

DR. GATSONIS: You're guaranteed --

DR. BAROLAT: -- that you will have to have --

DR. GATSONIS: That's what I thought.

DR. BAROLAT: -- serial surgeries down the line.

DR. GATSONIS: Yes. That's what I thought. Thank you.

The other question that I had was for -- when you were presenting the MDR data, you limited

the search to the IPGs, correct? Do you have similar data for the RFs, to see how some of these relative risks go?

MS. CAMERON: No, we didn't.

DR. GATSONIS: Because those RFs are relevant. I mean, if you were going to make a comparison between IPGs and RFs, I would have expected you would have looked at the RFs and you would have two columns of numbers there.

MS. CAMERON: No, we didn't do it. Not for the MDRs we didn't do that. Just for the -- we did it for the literature only.

CHAIRPERSON CANADY: Other questions from panelists? Thank you very much, ANS.

We'll now have a presentation from Mr. Bob Klepinski, the regulatory counsel for Medtronic. Go ahead, sir.

MR. KLEPINSKI: Good morning. I am Bob Klepinski from Medtronic. I'd like to talk in opposition to the petition today. Some of you here may think it unusual that a manufacturer would take a step which would appear to be asking for more regulation rather than less. And that's not our position.

If there was a general attempt on the

part of the FDA to simplify PMAs for these devices, and to do an easier route to market, we'd certainly work with the FDA and be all in favor of that. What we oppose is carving off this one indication from the rest of the implantable Class III neurological devices and putting in a separate class. And I'll talk a little bit more about my reasons for that.

Starting out, also, Medtronic feels extremely complimented by all of the things said by petitioner and by the FDA. In essence, what you've heard today is a fact that since Medtronic is good at this, and we've done it successfully for 10 years, we should simplify the system. In essence, we've had a system that worked well for 10 years, so we should junk it.

I think there's a lot of reasons not to do that, and that's what I'd like to talk about today is the -- the risk to patients that weren't discussed in any of the previous materials, and the risk to patients that we have to consider from active implantables.

And we have to put patients first here, and we have to consider what can happen to patients. That's our Medtronic focus. And I want

to look at some of the differences from a slightly different point of view than you've seen in the previous presentations.

Now, we're going to look at -- through this presentation -- through some of the pre-market PMA controls and their effect. We're going to look at some of the post-market PMA controls and how they have controlled patient risk, and also the MDR and adverse event reporting issues.

Now, the one big issue is the difference between an implantable Class 3 device, an active implantable as they are termed under the European community, and RF devices.

Now, we've heard today that the difference is a power source. That's sort of like saying the difference between a Conestoga wagon and a modern automobile is that there's a battery in the latter. I mean, it's true that there's a battery, but there's a lot more to it.

There's a lot of technology involved in this, and Medtronic, I have to say, is good at this. We've successfully done it. We worked under the PMA system. We know how to do this. And we also know how complex it is.

And the one major difference that I want

you to think about is that when you're talking about failure modes, the RF device is essentially passive inside the body. If there is any programming issue with the external device, if there is any malfunction, you take away that external device and you're left with a passive plastic encapsulated inert thing in your body.

With an active implantable, the active implantable is performing things in the body under programming control. And you cannot simply take away the RF antennas in an external device. It is working away inside your body. If the reason it is out of control, explant is the cure.

Now, these have not been an issue in the 10 years, the slice of data looked at here today. And the reason is we're darn good at this. We have not had problems in those areas. But that does not mean it's an issue that does not need control through the PMA process.

Now, some of the things that can happen are the device can malfunction. I mean, there can be circuitry issues. And somebody asked earlier today about pacemakers, and this is very analogous. There have been pacemaker companies that had circuitry issues that caused their devices to do

strange things. The same can happen with neurological devices and did happen in our predecessors.

Battery failure is not battery failure that is it's running down. I mean, it's a well-known phenomena. We know more about implantable batteries, I contend, than any other company in the world. There's one other real good manufacturer, but we know the most, we know how to characterize them.

But this is not an easy thing, and the battery leakage the FDA talked about can bring on patient effects that are very serious. And this is in a device which is operating on its own.

There can be programming failures. As we'll talk later, there's telemetring back and forth from a programmer to the inside, and the inability to program may leave you with a patient with a device that has to be explanted.

Stimulation parameters have been known to change on their own on some failed devices. And all of these can have various other patient sequelae.

Now, you've probably seen all you ever want to hear in the world about the difference

between implantables and external. So I'd like to skip through these parts fairly quickly.

But I want you to understand that the big difference is that with the implantable device, it is running on its own inside that body, and the control is through telemetry. There is no antenna to take away to shut it off. The device is operating on its own.

Now, an implantable device is incredibly more complex also than the RF device is. There is some circuitry in an RF device, but the difference here in having an implantable battery that you have to seal -- welding may sound like a rather benign topic to most of you, but sealing batteries is a very significant item, and the failures we'll talk about later resulted from that area.

Having circuitry that's going to stand up inside the body and operate on its own and keep telemetry out is a very difficult art. The sealing up of the can, the hermetic sealing of the exterior metal can is something we're good at. We haven't had failures in that, but there are pacemaker companies in recent years that had to have major recalls because of failures in sealing. These are not things to be taken lightly.

So, once again, an RF device receives their power from the outside. The circuit is a simple one to receive that power and send it through the body. When you take that RF antenna away, there is nothing going on inside your body.

In the IPG devices, the antenna is a radio communication sending not power but information in. The circuit inside is acting on its own, controlling the stimulation parameters. So you are dependent on the technology in that circuit.

So if there's a failure inside there, you can't stop it by simple external action. You have to put the programmer on and reprogram it. If the failure happens in a programming area, such as had in some past devices, then you cannot fix the problem; explant is the only solution.

So there is a degree of risk in active implantables that is different. And, of course, there's an internal power source, with all of the attendant issues, and there's an emergency stop. You have to have a way to do it through telemetry.

Now, I want to go on to talk about -- a little bit about the history of this. But we have to talk history briefly and issues that didn't come

up in the other presentations.

You saw a history chart that had notable events, among them the success of Medtronic in doing this. You saw one other mention of one other company in there. And I'd like to talk about that company and one other attempt.

In essence, to my knowledge, there have been three companies that tried to do this. Two have failed dramatically with FDA interaction. All of the data you've seen today is a result of the fact that Medtronic is good at this and it's our data. You've not seen anything to do with the two failures.

Cordis was mentioned here. Cordis is a pacing manufacturer and an implantable neurological manufacturer, like Medtronic, who was working on this around the same time as Medtronic started this project. They had serious battery failure problems. They had leakage problems. It caused the FDA to take fairly dramatic regulatory action against them.

Those products were removed from the market. The company was essentially out of business. It was sold to a pacing competitor and is no longer here. That device is gone.

The second company that went on to define an active implantable for neurological uses also had battery problems. That company had an IDE. When FDA went in for the pre-market approval inspection, part of the PMA process, there's a large 43 issue.

I don't know if you folks are used to seeing 43s. They are often a page, maybe two. I've seen some fairly big ones, but this --

CHAIRPERSON CANADY: I'm not sure everybody knows what a 43 is.

MR. KLEPINSKI: Oh. A 43 is the FDA observations of what they consider may be potential violations at a site, done by the field office. This 43 happened to the third company that tried to make these devices.

After that, there's a regulatory letter. The FDA terminated the IDE. The device never came to market. So, once again, we see, three people have tried to do this. Two have failed dramatically with FDA intervention. We have succeeded. All the data you've seen today has been about our success. So we don't believe, based upon that, that this system is ripe for a change to let anybody do this through the 510(k) process.

Let's talk a little bit about adverse events. Now, I'm not sure how the data was developed in this search. We went out after we saw this petition and did an MDR search. We did a search for spinal cord stimulation. We found there are some 400 or so mentioned in the petition. We found well over 2,000.

When we then went and split them into IPG and RF, as we thought we were using the same format as petitioner, they had a few hundred and we found 700. So there is a story here that you're not seeing.

And one is, I'll say exactly as petitioner did, you can't rely on MDR data for making your decision, because there's all kinds of things that cause MDRs. I mean, there can be different physician techniques. There can be patient interactions. There's a lot of reasons to file them, so there is a base number. You can't go by it, but two things to remember.

One, the MDR information you're looking at was Medtronic MDR information, on a system that worked well, didn't include the drastic failures. In fact, one of the things in this 43 was that they were not filing adverse event reports. And,

therefore, there are no adverse event reports for you to look at for that -- for the failed history.

But the thing to look at is whether, you know, when you look at the differences between what was found in the searches whether, indeed, is information before you. One of the issues you have to consider is that the statutory standard is not just the life supporting that was talked about for pacemaker devices.

There's two reasons to be in Class III. There's implantable or life-sustaining or supporting. If you're going to change an implantable device, the statute says you have to have sufficient information to show that special controls are going to be sufficient. And I don't think you have it in front of you because you haven't even seen the adverse history.

Now, one other issue to discuss today is what is being down classed? There has been much talk of this as being a device, but you're not talking here today about down classing a device. You're talking about down classing an indication.

Now, the IPG involved in this is a building block. Just like some of you asked about a similarity to a pacemaker, pacemaker technology

and all that we've learned about pacemakers and the difficulties are, indeed, the same in an implantable device. But just like a pacemaker is a building block for different therapies, the implantable Itrel stimulator is used in many, many therapies, all of which today are currently Class III, and many investigational things.

Now, the device today is used for chronic pain. We know of some physicians who are -- I don't know what company conducting a study, but I know there are physicians conducting studies on peripheral nerve stimulation with this device. It's used in deep brain stimulation. Medtronic has an approval for tremor. We have a clinical going on in Parkinson's disease.

There are physicians -- I'm not sure if it's in a the U.S. anymore -- but there are physicians who have been experimenting with deep brain stimulation for pain. There are studies going on in other countries for deep brain stimulation for epilepsy. There are many uses for this block.

So what you're being asked to do is not to down class a device today. You are being asked to take the entire range of things that this

implantable pulse generator is used for and taking one of the indications and moving it into a different class.

We think this is going to be a little bit of a difficult compliance issue for FDA, and it's going to change the way devices are used, and I'll talk about some of the implications. But remember, you're only looking at a slice of the pie in this petition.

Here's another continuation. We have a clinical going on for gastrointestinal pacing. There is a urinary incontinence approval by Medtronic currently with other clinicals going on. There is a fecal incontinence clinical. People have used this for sleep apnea, for upper airway pacing. This is the same building block.

So if you move this device to different controls in 510(k) world, you are not looking at all of the indications. You're going to have the identical device controlled in two different manners. And I don't believe that's practical for an active implantable.

The pain issues can be quite complex, actually. Remember, we're only taking a small slice of even the pain situation here and talking

about the indications that petitioner asked for. But there is many, many other pain issues that have always been treated as Class III issues, and the underlying devices Class III. Once again, you're going to have sort of a bureaucratic mess when you have all of these other indications retained as Class III and one slice cut out for a Class II.

So we'd like to now talk a little bit about the process, how something works through the PMA process. And please, please, please don't take this as an endorsement that all of the complexities of the modern PMA process are necessary in our opinion. We'd be glad to face simplification of them, and there is many ways to simplify them.

But we do not think that simply moving the Class II for this slice of this indication is an appropriate way to go at that. We should go at it for all of neurological devices if we do.

Now, there are many differences in the way PMAs are treated compared to Class II devices. And for active implantables, we still believe that this is the appropriate way. For example, all of the animal, bench, and clinical data review is much more rigorous. All of this is different in the PMA process from the 510(k).

I don't think, in our opinion, standards have come to the point where it can replace all of that. And I should take a moment to talk about standards, since it was stated earlier that we are a participant of this standard. We're a big believer in standards. We like standards. We participate in them. We participated in this one.

The question is not whether standards are good but whether it is in itself a special control.

Now, I know the Medtronic representative on the Standards Committee, and it was never his intent that this standard become a special control.

We have spoken with the FDA representative -- this panel -- in the past, with I believe now retired Mr. Mumsner? Munsner. And his intent was that this not serve as a special control.

We have with us Dr. Richard North from Johns Hopkins who was on the committee that did that standard, and he says it was never intended to be a special control. Now, this standard has things in it to which everybody should comply. But in no way was it meant to be complete and a replacement for the rest of this process.

Standards are good, but they are not at the point where they are going to replace active implantable controls.

Second, manufacturing controls are reviewed in a different manner for Class II devices than they are for Class III Devices. The Advisory Panel oversight is different. Class III devices -- the presumption is that they'll go to panel, unless the FDA can make a determination that you don't need to see it.

In Class II devices, the presumption is that you won't see these devices in the future, unless the FDA makes a separate determination that one of them should come here. It's going to be a different view with less oversight from the panel.

Facility inspection is going to be different. This is one of the things that I wanted to talk -- you to understand about the ramifications of the action. It is not simply a question of the approval process. It's not a question of how the PMA is obtained rather than the 510(k). Once it falls in one of these classes, other things fall out.

As you all know, the FDA does not have the resources to inspect every facility as often as

the statute requires. They just don't have enough people. It's a budgetary issue.

The FDA has established a risk position where it has determined certain classes of things that are inspected. And you do not have the same inspection on a Class II device as you do on a Class III device. Most Class II manufacturers are being, I think, on the average of something like five years inspected now, whereas the Class III manufacturers are getting their biannual inspections.

Additionally, there are inspection things built into the PMA process. Pre-PMA inspections are done on PMA products. They are not done on 510(k) products. Post-PMA inspections are done on PMA products and not on Class II products under the system.

So this falls into different areas, and I want you to remember that this site -- this site, the other failed company, was discovered on a pre-PMA inspection. Now, we contend that this company would have been on the market under a 510(k) system. And I don't think there's a special control today for active implantables that I've seen that's going to take care of that issue.

This would have been on the market, would have been out there in patients, were it not for the PMA process.

Additionally, labeling is treated differently. We are talking here about indications and not devices, as I said. So the FDA labeling review is critical. The FDA has labeling authority for approval for PMA devices. It can review labeling for 510(k) devices but does not have the same statutory degree of control. So when you're talking about an indication shift, it matters how much control there is.

Now I'd like to talk a little bit about what happens after a PMA is granted. Once again, the difference between Class III and Class II has sequelae. The things that happen to the device after entrance in the market are different.

For example, now, PMAs require annual reports. This includes commonly a review of advertising, it's going to have adverse event reporting. There's going to be a number of things in there that are going to help the FDA determine how the device is performing. That is not done in 510(k) products.

Post-market studies -- this panel, for

example -- I don't know if you individuals were on it, but the last time Medtronic was before this panel our neurological device it got a recommendation that we have a post-market study. And post-market studies, in my experience, have become much more common for panels like you to ask for.

That process is going to be different than the 510(k) process because now the FDA can, in a PMA grant, require post-market studies. That's there's going to be a different process.

The FDA's ability to -- in PMA grants to call these devices "restricted," which it has done for most Class III devices -- this has an effect on labeling and advertising. For example, restricted devices have to have a brief statement of indications, warning, and contraindications in the ads. 510(k) products do not.

Actions you have to move this into Class II are going to fall through the waterfall events and end up in different advertising controls. The difference between PMA supplements and additional 510(k)s is also going to be different, and it will be a different process, which I think will have a different degree of

control, and, once again, following on with the biannual inspections.

So there's a series of actions that are in place for PMA devices today that are going to go away. And it may not be obvious on just the class change from III to II from the approval process, but it's -- there's things after the approval process with which we're concerned.

And, once again, if you could wave your hands and make some of these regulatory obligations go away, you know, we'd be glad to participate in that process. But if so, it should be done with our eyes open on all uses of these Class III active devices and not this narrow use we're talking about.

So, and my conclusion is that you don't have the information in front of you necessary to make this decision today. You don't have a fair view of what the adverse events were in the past. You don't have before you the history of the two companies that failed at this.

Petitioner, I'm sure, knew at least one of these companies and has chosen not to include that, and I -- I believe it's keeping you from knowing the history of this.

This is a difficult, difficult thing. And because we've been good at it and succeeded does not mean that the process was bad. I think it's an indication that things have worked well under this process and you should continue it.

Do I have any time?

CHAIRPERSON CANADY: Yes, you have about five minutes left.

MR. KLEPINSKI: I'd like to ask if we could -- if Dr. North could come up. Dr. Richard North is a well-known neurosurgeon and author from Johns Hopkins, who has implanted all of these devices and knows the history. And I'd like to give him an opportunity to offer his opinion on the down classification.

Dr. North?

DR. NORTH: Thank you.

Dr. Canady, ladies and gentlemen, I've been involved in this area since I was starting out in neuroscience and neurosurgery as a biomedical engineering post-doc in the early '70s.

And now, as a professor of neurosurgery at Johns Hopkins, I have a clinical practice very similar to Dr. Barolat's. And I share a number of his opinions and also research sponsors. Like him,

I do research for both of these manufacturers.

I've been involved with the mechanical and electrical design, the systems engineering, the implantation, and clinical use of these devices, as well as their explantation. And that includes specifically the two devices referred to with internal batteries that are no longer available, and one which failed to make it to market. So I explanted some of the same devices that Dr. Barolat described.

I'm concerned as a clinician using these devices, and having patients referred to me who have them in place and who have problems, that the highest standards be followed. I'm concerned as a scientist that everything we do in the field be of highest quality.

And I'm concerned as one who has seen this field come a long way in the last 25 years that what is now a very safe and effective device, and that lets me do procedures as a clinician that are very gratifying, remain so.

It is the way it is because of excellent quality control on the part of manufacturers and on the part of regulatory bodies. And I think the PMA process has, in this sense, served us very well.

So I'm just here to speak for continued excellent quality control on all fronts.

Thank you.

CHAIRPERSON CANADY: Thank you.

Panelists have any questions for Mr. Klepinski or Dr. North?

DR. HURST: I have one question.

CHAIRPERSON CANADY: Yes.

DR. HURST: This may be from the regulatory representatives' standpoint. Did I understand that Medtronic is using the same device for the deep brain stimulation?

MR. KLEPINSKI: The IPG is the same, yes.

DR. HURST: Okay. I see.

CHAIRPERSON CANADY: Come to the microphone, please.

MR. KLEPINSKI: I can't answer technical questions if you get into details, but the IPG itself is a building block. It's used for all of these various therapies.

DR. HURST: I understand.

MR. KLEPINSKI: And it's also used by physicians for their own research. Many physicians will try things that are off label. Occasionally,

they'll have a patient that requires it and they'll use it for something off label. But they'll also do their own studies, get their own IDEs to study using the same building block with a different lead on to some other parts of the body.

I mean, literally, Medtronic is working from head to toe with this device. And all of those things are Class III currently. You know, the question I was concerned about is, when a physician could then -- who is going to do a clinical by the same device as a Class II device or the same device as a Class III, we would not have the same treatment, then, for the other investigational studies.

And I think that would be a very difficult thing to control, but it's the same building block.

CHAIRPERSON CANADY: Other questions for the representatives of Medtronic?

We're going to close that portion of the meeting now and go to the open panel discussion. Dr. Edmondson has reviewed this topic for the panel and has a presentation.

DR. EDMONDSON: Okay. Thank you, Dr. Canady.

The presentations from the petitioners and the protester is enlightening, and I mean that sincerely. And in that context, my position and task here is to speak from the mind's eye of a treating physician, one who has seen patients with chronic pain and who have had an opportunity over the past 10 years or so to observe these devices used for intractable pain.

Let me start with really how this came about, how the -- what -- how the rationale for using neuromodulatary stimulation for pain control came about. And this was born from, really, theory -- theory presented by Melzack and Wall in 1965, the Gate Control Theory.

And in this theory, based upon neurophysiological animal data, Melzack and Wall devised a -- proposed a theory in which they outlined that A-fibers, when stimulated, can block the conduction of C-fibers or inhibit the input that C-fibers would make to the cells in the spinal cord that goes to higher centers and tells the brain that pain is occurring.

Since the inception of these devices for use in the clinical arena in 1967, research has demonstrated that stimulation along the dorsal

column can influence a number of different processes in the spinal cord, including the release of neurotransmitters, GABA, the reduction of excitatory amino acids, and, in fact, potentially the direct blockade of C-fiber conduction based upon direct interference from the stimulation itself, rather than through A-fibers.

The point of this is that theory brought us to this technology, and that theory has also brought us to the notion of the more you know, the more you don't know. And we have learned through this that the processes are very complex.

But the bottom line is that over time it has been observed that spinal cord stimulation can provide relief in a number of different clinical scenarios. We're asked to look at the indication for chronic pain. The literature is really robust for a number of other indications, such as peripheral vascular disease, angina pectoris. There is a lot of European literature regarding these entities.

There is also some literature for movement disorders and spasticity, although with really mixed reviews.

Now, in the context of trying to discern

risk and class, reclassification, and that sort of thing, I'd like to revisit that after we have looked and reexamined some of the data that you have heard about from our previous presenters.

I've had an opportunity to review a small portion of articles, namely about 35 articles out of perhaps over 200 articles that are known to be out there, addressing how these stimulators are used, what the efficacy is, and cited risk.

Now, of these studies, I call your attention to Boggi, et al., an Italian study, where over 400 patients entered the study, and 363 received spinal cord stimulation. The vast majority of these patients had either back pain or RSD.

The point here -- and I'm not going to go through reading all of these iterations of different responses and risk -- but initially, the response is roughly, in this study anyhow, 87 percent of the patients had pain relief immediately. Two years later, 58 percent had relief.

The other articles cited in the summary provided to you, my colleagues on the panel -- without going through them individually, I should

underscore that in my own practice, in collaboration with neurosurgeon, that we have found also an attrition over a period of two to five years from anywhere from 75 percent response rate -- with pain relief greater than 50 percent -- dropping to about 60 percent.

Nonetheless, even in patients who report that they get less than 50 percent relief, they are unwilling to turn the stimulator off or have it explanted. So, obviously, in that context some folks, even though they don't meet criteria for relief, which is 50 percent or better, are experiencing some benefit and would rather have the stimulator in place.

Now, with regard to risks, it varies significantly in terms of data in the Eighties versus data in the Nineties. It also varies according to the series because some of these series had only 40 patients, others had 70, some, a little over 100. The vast majority of publications are really within that range. Very few are several hundred.

Now, the most common complication is lead migration or dislodgment and that is the reason for loss of pain relief.

With unipolar leads, this generally means that you have to go back and reposition them.

With leads that have several electrodes, on the other hand, with reprogramming, the incidence of having to go back, do another surgery to reposition these leads, is reduced.

Likewise, for the octode electrode, namely with eight electrodes on each lead that is available in the external system, the use of reprogramming actually has greatly reduced the need to reposition those leads because you have several different permutations to work with to salvage the loss of coverage for pain relief.

But we are still faced with some malfunctions that can be quite striking.

However low the incidence might seem, on a personal level when attempting to reprogram the simulators and dealing with individual cases, we are again reminded of the complexities of all of these devices and how glitches in programming, circuitry or whatever it might be, can be multiplied.

The incidence of infection roughly, in most series, is two to three percent. And again, in earlier years it was relatively higher in some

instances because some leads were placed intradurally, some patients had multiple attempts because of epidural fibrosis. And those patients are actually, the incidence rate for complication is higher and curiously, it is within patients who themselves has had numerous surgeries, more than two, to rectify the problem.

So, that is just to give you an idea, in terms of total numbers, what that reflects.

Now, basically the efficacy of these devices is well-established and that is why the currently existing ones are FDA-approved and have really the FDA stamp of approval with the internal device being a Class III.

Now, I call your attention, my fellow panel members, to the last page of my handout.

Really, the crux of our deliberation here is whether or not the existing body of evidence in the literature is sufficient to justify reclassification.

Now we have really over 250 articles, most of which are case studies. We are dealing with currently available effective devices that have comparable risk. But I call your attention to a couple of nuances.

Recently I had a patient whose stimulator would sporadically turn on and cause electric jolts and, I think in part because, the battery life, it's near the end of the battery life.

But in any event, attempts at adjusting the stimulator inadvertently caused an increase in the intensity of stimulation and that person could not turn it off. So, ultimately, that required explantation to rectify the situation.

Although this is not a commonly experienced complication, new circuitries, the fusion of existing circuits, batteries and other components, in that setting we have to ask whether or not combining these modular components into one is equal in effectiveness and with the same degree of risk.

Basically, I would just like to stop there and open to the rest of the panel for discussion.

CHAIRPERSON CANADY: Thank you. As we have the general conversation, just so you know, Dr. Bowsher is going to start getting ready, putting the questions up for us, so don't get distracted by that.

General comments?

Dr. Walker?

DR. WALKER: Since some of these engineering issues, I don't mind going next. We have heard there were two firms that had pre-market approval for implanted pulse generators and one that worked on an IDE, in fact there were two companies that worked under IDEs, one of which worked very successfully but decided there was no market potential, and made a very safe product that was very good.

We used those at our institutions in the early Eighties. But Medtronic came out with one that was programmable and this one was not programmable so that firm left the market.

So, to set the record straight, that only Medtronic can make a proper IPG, other companies have made them, but Medtronic has made them with more bells and whistles and the market demanded bells and whistles.

In the early Eighties when we first started working with these, the issues were battery life and integrity of the hermetic seal surrounding the titanium case.

In the almost 20 years that have ensued,

my opinion as an engineer is that the technology has improved and these are no longer the cutting edge problems that they were in the early Eighties when the two devices that received PMA and Class III came out.

The question that we need to look at is whether we still need a high level of pre-market scrutiny for implanted pulse generators now that the most common failure modes are external to the implanted pulse generator.

The most common failure modes are lead migration, lead wire breakage, electrode migration, and those aren't parts of the building blocks that we are talking about today.

The petition that Medtronic reviewed points out a lot of things that have gone wrong under Class III regulation.

I didn't hear the part, of why is it that if, if all these bad things happened under Class III, why is it, wouldn't they happen under, you know, what's so great about Class III if all these bad things happen, that Class II, the same damn things wouldn't have happened any way and I didn't hear that.

I did hear, and I have a question for FDA

about this, about that Class II manufacturers are only inspected once every 5 years. Is that true?

MR. DILLARD: Jim Dillard. I guess I need to make a comment on that.

While I am not from the Office of Compliance I have to give a little bit of background that, with the resource crunch we are currently under, much of what we are doing is prioritizing the kind of manufacturers that we inspect and how often we inspect them.

Now, irrespective of whether or not it is Class II or Class III, those high risk, implantable kinds of products tend to get more scrutiny and they get inspected more often, too. And that again, is irrespective of whether or not they are Class II or Class III.

Now, the reality of the inspection situation of all of the Class II devices -- now we will take out Class III, because Class III, the inspection there is pre-inspection, there is post-inspection approval, or post approval inspection, there are the types of things that Medtronic spoke about.

In the Class II regime what we get is that hierarchy of how often something will get

inspected. There is a number of factors that go into it.

The reality is, is that unless you are in one of the high categories that we tend try to inspect more often, if you are in either a middle or lower tier in terms of risk, reports, how many failures you have been having, a number of things could kick it up into the higher category, a lot of times the inspections now are happening every five years,four to five years, somewhere like that on average.

So, just because this product type, if it were down-classified to Class II, there's a number of things with any individual manufacturer might cause them to be inspected more often.

So, I wouldn't call that a general rule, but I would say that the Class II kinds of products are being inspected much less frequently than do Class III products.

DR. WALKER: Do we include as a special control the same biannual inspection that other implanted pulse generator manufacturers were subjected to?

MR. DILLARD: I think if you believe that that's important that you could put that in as

recommendation, yes.

CHAIRPERSON CANADY: Other questions in general discussion? Or comments? Then we are going to begin our question-by-question discussion.

Question one is up, I believe. Dr. Gonzales, maybe we will go the other way around and give Dr. Hurst a break for being the first guy always.

DR. GONZALES: Well, the first part of the question, "Do you believe that there are any other additional risks to health besides those identified in the petition?" I do have a concern that if using the statistics or the numbers ANS has presented when they talked about the MDR incident reports, 25 percent of the 400 plus MDRs were in the "Other" category.

So, the real question is, is 25 percent "Other" enough of a safety issue if those "Other" incidents were in fact significant enough to be a safety issue for the patient.

So, I have a real question about the unknown 25 percent "Others" of reports that have been occurring. And until that 25 percent is better explained, and of course that's talking about the 400 plus rather than the possibly 700

reports that may also possible, I am concerned about that.

So are there additional risks? I just can't answer that. I am not sure we have enough information. So that's the first part of the question.

The second part of question one, "Please include in your discussion whether Class III totally implantable spinal cord stimulator devices utilized by the same population as Class II radio frequency coupled devices?"

Right now it does not appear that the patient population, that is to say that the implantable pulse generator population is less or more complex as far as the patient selection. So, it does not appear that there is a difference.

There are differences though in terms of patient effects that haven't been stated. I am not sure that they are that significant, but could be.

For instance, with the radio frequency, tactile stimulation occurs with the placement of the external radio frequency device that, with tactile stimulation, was some of the indications as far as pain.

Since the device has to be placed

directly on the skin in roughly the TAT 10 dermatome, there are pain states such as reflex sympathetic dystrophy arachnoiditis and spinal cord central pain where the pain can actually spread and this can happen spontaneously over time irregardless of the stimulation and therefore, radio frequency contact could in fact influence.

But other than that, which is responding more to the radio frequency rather than the implantable, I don't think there were many major differences in the patients.

You could speculate that because it requires more attention that the psychologically impaired individual who should be screened out to begin with might be more complex of a patient.

So, I don't believe there is a difference in complexity, just kind of looking at it overall.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: Based on the universe of information that we have received, it is difficult to answer this question. I don't see any evidence that, one way or the other, for this. I would have liked to see some kind of comparison between IPGs and the other kind of devices. But that sort of

comparison is really not there in terms of numbers. I would say, however, the following, that what we know about the IPGs is based apparently on one IPG which is out on the market.

So, I don't think you could make a case or a prediction as to how a different IPG by a different company that gets out on the market would operate.

So, from that point of view, there may be additional risks that don't apply to all the IPGs, but they apply to specific ones.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I don't have any comment.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: On the first question there are no additional risks. I think ANS has done a good job of identifying them.

On the second part of the question, for this indication, it is the same patient population and I think we need to be very specific about that because the Itrel, being such a wonderful universal device, is being used in other indications and other applications as well. And that's why we need to be very specific there.

For the third question, "Are the risks

unique to the Class III population?"

The only unique risk is the greater difficulty in turning off runaway stimulation, but we haven't seen a great number of reports of runaway stimulation with implantable pulse generators which are more easily stopped than the RF system.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: No additional comments.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: No additional comments.

CHAIRPERSON CANADY: Any other comments?

Dr. Edmondson?

DR. EDMONDSON: Yes. Basically, the population for both types of stimulation, RF or totally implanted is the same, but there is one qualifier. Patients with primarily back pain, midline, truncal pain, appear to do better with programs that offer several modalities and multiple leads.

So, the matrix system, for example, of one of the companies here, the other system with eight leads, and actually if you put two different leads, two different stimulator leads on with eight electrodes each, those seem to offer an advantage.

The external system seemed to offer an advantage to selected patients who have primarily truncal pain rather than limb pain.

But generally, for both devices, if you have limb pain you are more likely to have relief for the long haul compared to those who have midline pain.

With regard to risk, I think it is already stated and addressed. There are no additional risks.

And Class III, though I should mention, that if you have disagreeable stimulation, a pulse generator that isn't working, a failed battery or whatever it might be, you just take the strap off and you are all set.

So, a brand new system with all its nuances may have some problems with it that would require an incision, so that has to be taken into account.

CHAIRPERSON CANADY: Dr. Hurst?

DR. HURST: Nothing additional.

CHAIRPERSON CANADY: Any other general comments regarding question one?

We could have question two?

Dr. Gonzales?

DR. GONZALES: "For all of the risks to

health identified by the sponsor, are the proposed special controls adequate?"

The issues come down to really the abnormal stimulation that may occur, the battery running out and the replacement of the battery.

And finally, the concerns that have been brought up about manufacturing, and regarding the manufacturing, I can't address that. I think there are other people here who are experts and can address that. So I really can't address that.

But, as far as the abnormal stimulation and the battery running out, this is placed into and known ahead of time, and patients are warned that this is part of the risks or the problems associated with this particular stimulator type, and so it comes down to the risks of the surgery and repeat surgery, and does that warrant the Class III versus the Class II.

So I think those have been discussed and I think those have been identified and I don't think that at this point in time, special controls other than those that have already been identified, are necessary.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: No additional comments.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: Yes. I'd just like to make at least one comment on the FDA inspection issue that came up earlier.

The law actually has not changed. The FDA is supposed to inspect all facilities every two years. It doesn't happen and they have turned to more of a risk-based looking at things.

But, in fact, all manufacturers are still required to comply with the quality system regulations and many different things generate inspections and the rate of inspection is actually endemic as much as to where your facility is located and how busy the Division is that is there, as to anything else.

So, I think that we need to be aware that we all have to follow the manufacturing regulations as to how we make our product and there are a lot regulations on us to do that.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: As I reviewed the proposed labeling and special controls from ANS, unfortunately I found many shortcomings and I kind of hate to get us into the business of wordsmithing on Friday afternoon. But at the same time, if we

don't look at them -- So, I thought what I would do is make a foil with the problems that I have, and maybe we could go through all of them. Is that okay?

CHAIRPERSON CANADY: If you use the microphone, Dr. Walker.

DR. WALKER: Okay. The first one, I guess we can read two things at once. The place where we are looking is in the ANS petition, page 17, section D. One of the proposed labels that they include is the phrase, "Adverse events include undesirable changes in stimulation," and it seems to me if this is going into a patient or physician booklet, it seems a little bit vague or it needs a little bit of elaboration as to just what undesirable changes in stimulation means.

What I would like to suggest is that we point that out to the FDA staff and perhaps suggest that they work with the sponsor or ANS to get that changed rather than we word-smith it here on Friday afternoon.

I don't know, what is the procedure? Go through them one at a time? How do you want to do it?

CHAIRPERSON CANADY: I would go through

them all at once.

DR. WALKER: Go through them all? Fine. The second one, section E, the original wording is "adverse events include possible pain at the implant sites" since there is both and electrode implant site and a pulse generator implant site.

I think that should be tightened up to emphasize that the pain is at the pulse generator implant site perhaps due to anode break excitation or some phenomenon like that.

At section F there is a phrase "adverse effects include allergic response." This is the section on biomaterials and I suggest we include the phrase "to the materials used in the device."

And then in the section on other adverse events, "other adverse events include erosion," and erosion, again, seems pretty broad and we might want to consider saying skin erosion over the site of implantation rather than just the more broad phrase, erosion.

CHAIRPERSON CANADY: Any other comments you would like to make?

DR. WALKER: Do we want to talk about including, as well, some phrase, something about inspections and annual reports? Because I think

those, the inspections and the annual reports that Medtronic pointed out are important.

CHAIRPERSON CANADY: I think that is very reasonable to discuss at this time. Yes.

DR. WALKER: Okay. That's it. Do you want to discuss this?

CHAIRPERSON CANADY: Okay. Dr. Ku?

DR. KU: I think we pretty much agree that spinal stimulation works, so that's not an issue with me.

The main question is, is the power device, whether it is inside the body or outside the body, and it seems to be more of an engineering question, whether manufacturers can reliably and with ability to repetitively produce devices that don't fail. That is the bottom line.

The question is whether or not the current regulatory procedures as far as good manufacturing practices and inspections to make sure those practices are followed, as well as obviously proper design of the circuitry so that it is designed not to fail or has been tested adequately so that all the bugs have been worked out, whether or not the programming has been tested, so that all the bugs have been worked out,

seems to be the main question.

And I am a little unclear as to what the current state of the art is as far as the materials. Could you address that?

DR. WALKER: In terms of biocompatability?

DR. KU: Biocompatability, whether or not it is very difficult to design a system that is relatively fail safe, or it just takes a bunch of smart engineers who work real hard and do it?

DR. WALKER: At the risk of being facetious, smart engineers who work hard can do almost anything.

Having said that, the basic materials, and of course we don't know what ANS is proposing to use as their materials, but assuming it is similar materials to Medtronic which is a titanium case and either a urethane or Silastic coated lead, those materials have been around for 25, 30 years and seem to be fairly stable.

With respect to reliability certainly there have been even RF coupled systems, particularly the frenetic nerve simulators and the cochlear prostheses that achieved tremendously high degrees of reliability.

I am not worried about whether that's theoretically possible and it would be left to the design controls that would be imposed on ANS to be sure that they achieve the same high degree of reliability that other people in this business achieve.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: I'd just like to remind people again that we are not talking about the approvability or the not-approvability of the ANS product, but whether these devices fit the criteria for a Class II device versus a Class III device.

So, I think we need to be very careful in how we look at this and how we are discussing this.

DR. KU: Right. We are mainly looking at spinal stimulation.

MS. MAHER: Right.

CHAIRPERSON CANADY: Any other comments, Dr. Ku?

DR. KU: No.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: I am basically pretty comfortable with the information that has been presented here and I think the points that Ms.

Maher has brought up are right on target.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Having said that, I think I am somewhere in between. I think my uneasiness relates to probably more the bells, whistles and engineering and the assurance that really external versus internal pulse generation, whether or not that distinction is a critical one, because of the safety of removal of the device. An internal device would require an incision and removal in the event of malfunction.

Currently available simulators have demonstrated rather low incidence of pulse generation problems and circuitry problems and software problems.

But nonetheless, in this milieu of providing competitive advantage in the marketplace, that is what has made these two companies, for example, survive this far and each time you redesign you create new software and programming, and put things together, there are nuances that may be unforseen.

CHAIRPERSON CANADY: Dr. Hurst?

DR. HURST: I have no comments.

CHAIRPERSON CANADY: Any general comments about question two?

Question three?

DR. GONZALES: "Does the information in the petition and your professional experience support reclassification of the device?"

I'll bring up the question I have again of the 25 percent "Other" group.

This may be in fact enough to question the safety, if those 25 percent MDRs were related to battery, battery failure, battery problems, the power generator, and so I would also ask Dr. Gatsonis, statistically, since that is your expertise, the kind of numbers, the 25 percent, if that also is of concern to you?

DR. GATSONIS: Well, there is no denominator in those MDR data so it is very difficult to know what they represent. I have no idea, I don't think anybody has any idea whether this is a large number or a small number compared to all the implants that were made. So the only thing that you could do with that data is compare IPGs to the relative rates within IPGs to within RF. But we don't have those.

We don't have any data for this kind of discussion. It is somewhat bizarre.

DR. GONZALES: And unfortunately, that's

the crux of the problem right now. As long as there is a question of 25 percent of the MDRs being "Others" that may in fact involve battery, that may in fact distinguish this from "Other" radio frequency, it is a concern and I don't know how to respond either.

So it may be from the manufacturing, the abnormal stimulation run out, the replacement, all of that appears to be an acceptable aspect of the implantable that is in fact controllable in such as way that a Category II is appropriate.

I still have the one question about the 25 percent and if those are in fact related to battery function and that hasn't come out. I'd like more information. I can't answer that question without more information about the 25 percent.

CHAIRPERSON CANADY: Dr. Gatsonis, any other comments?

DR. GATSONIS: Based on the information of the petition, I cannot really think that this reclassification should go ahead.

I don't see that there is enough evidence to support this. And unless the evidence is there, I am willing to be swayed by the argument

that says that there are a lot of implantable devices out there that look very similar to this and they are all in the third category, and in Class II and I don't see why we would take one particular one and move it this way, in the absence of data and in the absence of that kind of convincing information. So, until that is done, and those devices are looked at more generically, I don't see why, in this specific case, we need to move it.

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: Yes. I think what this question is asking, and I actually, from experience of course, can't answer that, being a lawyer not an MD.

But I think what we are looking at, is the law asks this panel and the FDA to use the least burdensome possible way to get products on the market for the intended use that they are going at.

So, you can pull it out, if in your professional opinion spinal cord stimulation for this intended use falls in the Class II, then it is perfectly okay and I think this panel needs to evaluate what you know about spinal cord

stimulation as a whole.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: In general, I agree with Sally. Our job is to look at what is the lowest classification that will still provide reasonable safety and effectiveness and I believe that is Class II.

I am not bothered by the fact that there would still be some Class III indications, deep brain stimulation as an example, because that is a newer application and not as time tested and proven as spinal cord stimulation is. My one remaining area of concern, and of course this is not a life support application, either. My one remaining area of concern that still remains is why pacers are all Class III, and these devices are being proposed for Class II when they share, essentially, the same technology.

If the reason pacers are still Class III is just because they are life support, then I am comfortable moving this to II, but if there is a technical reasons why pacers are still Class III as well, then perhaps this should remain in Class III and maybe someone from FDA could answer that question.

CHAIRPERSON CANADY: Mr. Dillard? You are the lucky one.

MR. DILLARD: Jim Dillard, I get all the tough ones. One of the significant differences, I think Dr. Walker, that you bring up between the two, and I would have to agree, is that one is life supporting and the other product and the other use for that product, is not life supporting.

One other thing I might just clarify a little bit here, too, because one of the issues that was brought up by one of the presenters was that specifically you all are looking for an indication for use and I need to provide just a little clarification on that, because we at FDA define a medical device as the article plus what it is intended to do.

We can't separate those two. Those two go together. So, when we talk about anything we classify, anything you see in our Code of Federal Regulations, it includes a product description of the article and then an intended use, what it's intended to be used for and so, we can't separate those.

So, in this case we are asking you for a specific situation of a product and how it is

intended to be used. Is there enough information to support reclassification; that is what the petitioner is asking you, and then what are the level of controls that can reasonably control for the safety and effectiveness of the product and I think that's what the legal obligation is, for us to do as well as I think, your recommendations.

So, whether or not, Dr. Walker, there is anything else other than the fact that there is a significant difference between one is life supporting and one is not life supporting, I don't think that we have gone into the detail to really describe between the two, because again, I think my point of this device, how it is used, and the data that is available for this device and this use, is the standard by which we judge reclassification.

Not compared to where other products with other indications might be based on their known information, the knowledge on their product and how they're intended to be used.

CHAIRPERSON CANADY: Other comments, Dr. Walker? Dr. Ku?

DR. KU: I'm pretty convinced that the indication as far as spinal stimulation is a good one, that it works.

The part that really bothers me about this petition is I don't think they have shown the data that would make it possible to easily and reliably produce a component that would have a low failure rate.

If that can be done, as Dr. Walker suggests, relatively easily, then I think it is quite reasonable because it is just an engineering issue. And if you can, with regular manufacturing controls, assure that the failure rate of this product is going to be low, then I don't have a problem with that. But on the available data that is presented in the petition itself, I don't have that evidence.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: It is getting tougher.

I think a lot of my thoughts have been represented. I think Mr. Dillard's comments were extremely helpful because being able to look at this within those brackets proposed by ANS provides me a lot more comfort with saying that this could potentially fit within the realm of a Class II.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: Okay. I think I would

echo Dr. Ku's comment that largely it pivots around the whole engineering issue because I think that there are enough special controls there, but given current technology is there enough quality assurance, after going through those hoops of special control, that would make this, that would assure that this would be a relatively safe new device, totally implanted.

CHAIRPERSON CANADY: Dr. Hurst?

DR. HURST: I agree with Mr. Dillard's remarks. I think that when we are talking about a device as well as well as an indication that's linked, I think that is a very important concept, at least for me, to keep in mind, and I think that the special controls that we have discussed already seem to be something that we can make this very stringent, if we need to. I other words, I have a lot of faith in the ability of these special controls to maintain relatively high standards of safety and efficiency.

I think based on that, and the fact that we are talking about a device and an indication, I think I could lean towards putting this into Class II.

CHAIRPERSON CANADY: Any other general

comments about question three?

Then we move on to the final question, question four.

DR. GONZALES: "If you believe that the Class III spinal cord stimulator device should be reclassified to a Class II device, please discuss the appropriate indications for use for the totally implanted spinal cord stimulator device."

I do not believe there should be reclassification from a Class III to a Class II device because of my concern regarding the safety issue and the unknown regarding the MDRs that have already been brought out.

CHAIRPERSON CANADY: Dr. Gatsonis?

DR. GATSONIS: Yes I do not believe the reclassification should go ahead, so --

CHAIRPERSON CANADY: Ms. Maher?

MS. MAHER: No comment.

CHAIRPERSON CANADY: Dr. Walker?

DR. WALKER: I believe we can reclassify it and that the fairly tightly defined and limited indication that has been proposed is appropriate.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: I agree with Dr. Walker. I am a little disappointed in that the petitioner has

not presented the data to show that it is easy or reliably possible through standard manufacturing to achieve these conditions of reliability. I think they should have done that.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: No additional comment.

CHAIRPERSON CANADY: Dr. Edmondson?

DR. EDMONDSON: If I could stay in suspension for a little while to decide and perhaps the FDA could help me out a little bit.

CHAIRPERSON CANADY: Well, we are going to have a little session here for clarification for them.

Obviously, there are some questions that I would clarify if I were these people.

Dr. Hurst?

DR. HURST: I have no additional comment.

CHAIRPERSON CANADY: Any other general comments regarding question four?

If not we are going to offer the opportunity for the presenters to clarify issues.

We will start with Dr. Johnson.

If you have any comments you would like to make?

MR. JOHNSON: Thanks again. Drew Johnson; you all know me by now.

Just a couple of quick comments regarding the opposition's concerns, and they do make a fine product and I do believe that, given the opportunity for reclassification, given the controls that we have proposed, given the FDA and their ability to choose whether or not devices goes to market or not, I think that this device should be reclassified.

But I had some problems with a couple of things regarding manufacturing and reliability of devices and so forth.

And I do believe that the use of special controls and the use of risk assessment would come up with technological answers to questions, and I think they have already been answered, like the runaway stimulation situation. Magnets are now available. A simple re-switch turns off the device.

So, that is all I have to say.

CHAIRPERSON CANADY: Thank you. Mr. Klepinski?

MR. KLEPINSKI: Yes. I still think that the key issue under this is what has been hinted at

from this side of the table, and has never been addressed. The issue has been talked around, but never addressed. There is nothing in the petition that truly addresses the difference of going from an implantable and the risks involved in designing an implantable and the risks of controlling it through RF.

Dr. Walker said this is an engineering change and is workable. We agree that we have done this. It is possible. But it has been done under a quality control scheme that is quite complex, and has been closely controlled by the FDA.

The success in doing that under the current system does not mean that it is going to fall in place automatically for everybody.

I contend that active implantables are different from other devices.

That is why, in the European system, active implantables are controlled under a different directive than the rest of medical devices. That is what we are talking about today. Not the effect of the lead in the spine, all the talk has been about the therapy and we'll say the therapy is generally the same, the contact in the

spine, the same. The difference is the difference between an active implantable and an inactive implantable and there's been nothing in the petition that talks about any specific special controls that are going to deal with active implantables, as far as the manufacturing.

In Europe, when these are controlled, this ANSI standard is not used as the standard for under the CE mark. Actives are treated differently and inspected differently by notified bodies in the United States, active devices have always been in Class III. To the best of my knowledge, this would be the first implantable moved into Class II.

Now, this may be the wave of the future and you are going to move all of these various neurological therapies down. But I do not think that you have in front of you the information needed to fulfill your statutory obligation.

That is, the statute says you move these into Class II if you have adequate special controls.

The special controls that were shown to you, if you read them, talk about EMF interference. They talk about things whether your microwave is going to interfere or a theft detector, they talk about labeling. But they do not talk about

the manufacturing and testing of active implantables.

So, that that information is not here and I don't think that, you should be making, in the absence of it -- I don't want to sound like I know more than you about the manufacturing of pacemakers; we have experts that do that. I don't want to make it sound like there is black magic here. But I want you to understand that the whole system that's gone out around protecting the active implantables is different from the controls that you've seen in these. You can't simply go out of here saying that you will throw a few more things into the special controls and take care of the whole rest of the PMA scheme. I mean, there is a major difference here.

When we talk about, a runaway is not a problem but not anymore. That is because we worked at this for 20 years. It happened to pacemakers.

There are still failure modes out there today. There is, as I said there is a pacemaker manufacturer that had a sealing problem with leakage, a hermetic sealing problem in recent years. Within the last seven at least, I think

within the last five.

I am not saying that we are the only ones who can do it. There are other people who can do this, or other quality manufacturers out there making pacemakers, for example. What I am saying is it is real darned hard, as they say in the TV ads, don't do this at home. I urge you, unless you find a way to replace the current system, not to move an active implantable into Class II.

CHAIRPERSON CANADY: Dr. Bowsher, do you have any additional comments to make?

DR. BOWSHER: No.

CHAIRPERSON CANADY: Okay. Then we're going to move to our favorite, go ahead Dr. Edmondson.

DR. EDMONDSON: Just another question to the FDA itself. I think a little bit of history could be used as a foundation before we move the motion to vote on this. In terms of why was the implantable device was placed in Class III in the first place, in the Eighties? Okay. And even though we have more clinical data over the last 15 years, vis-à-vis the special controls that are currently in existence, really how is that improved

compared to 1984, let's say?

CHAIRPERSON CANADY: Mr. Dillard?

MR. DILLARD: Could I ask for just a moment while I confer with a colleague, real quick?

CHAIRPERSON CANADY: Sure. If we could have the forms while we're conferring?

MR. DILLARD: Okay. I'm back. Jim Dillard. Dr. Edmondson, could you maybe take one more shot at it? Because I think I have your answer, but I want to be sure to hit it right on the head.

DR. EDMONDSON: Okay. Whenever it was, I guess '81. When the first application was made for a totally implantable device under Class II 510(k), it was suggested that it be processed under PMA. Okay.

Now, over the last 15 years or more there is a growing amount of evidence regarding, we have a larger denominator to deal with in terms of what the risks are for this particular device.

But we are not dealing with a large number of competitive manufacturers, and that is part of the problem. Now, over this time, what sort of special controls, and we have the special controls that are proposed. But how does

that work in the whole FDA mechanism here? What is the big difference between past and present tense?

MR. DILLARD: Well, let me try to balance a discussion or a description about the past and present, and try not to be too leading.

I certainly don't want to do that in this circumstance, I want to give you some information so that you can deliberate.

You have heard about pre-amendments, post-amendments, Class III devices, from the training and everything else. What I can say is that, from the standpoint of what the advisory committees back in the late Seventies and early Eighties looked at were the known products that were on the market at the time, in order to give a classification recommendation. At that time, what was on the market were the RF-coupled kinds of devices. There was not an active, implantable pulse generator for this indication for use on the market, prior to May 28, 1976. So, when one came in after the original classification went through, and the manufacturers claimed equivalence to the best predicate devices they could, which were the RF-coupled devices. Same indication for use, but different technological characteristics.

The way we analyze through 510(k) whether something is substantially equivalent or not substantially equivalent, there are three reasons why something is not substantially equivalent.

Either it has a new intended use, it has different technological characteristics that raise different questions of safety and effectiveness, or data, when you compare it to a device on the market demonstrates that they do not perform equivalently.

I would venture a guess, even though I don't have the letter in front of me, that the reason we found the active implantables not equivalent to the RF-coupled devices was, at the time, we believed that the technological characteristic, the technological change of having the battery self-contained and the generator implanted in the body, raised different types of questions of safety and effectiveness as compared to the RF-coupled. Questions as simple as all the ones you are discussing. Infection differences, we didn't have a can that was being implanted in that kind of situation. Controllability, battery leakage, battery drain, all the issues that have been discussed here today,

were new then. So, our regulatory decision was based on the newness and the new types of questions at the time.

Congress envisioned, even when they gave us the medical device amendments back in 1976, a process of reclassification as more and more knowledge became available on products.

Now, that doesn't only pertain to reclassification from III to II, but ir pertains to reclassification from II to I, II to exempt, II to I and I to exempt. I mean there are all these permutations that are possible. And so, the whole legal thought process, and legislative thought process, was that, as we gained more experience and different ways to look at risks and control for risks, that reclassification was an option for a manufacturer or manufacturers to move products to the most appropriate class based on knowledge and based on our ability to control risks for the product.

So, what has changed over 15 years, which I think is really your question? Well what's changed is, perhaps, and this is really, I mean you all today, will have to judge this, and we at FDA will have to judge it when we try to make a

final determination on the petition, but do we know something about the risks, can we characterize the risks, is there data that supports what those are and what we can say about them, which is really the statutory standard that we have to look at, and then can we control for those risks with either special controls that we have available to us or special controls that can be proposed that need to be developed prior to moving forward with reclassification and that's all envisioned under the scope of the legislative environment and our regulations for reclassification.

So, 15 years has changed it. Just the fact of the matter that we have 15 years that there is more data so we have to look at, I am not saying it supports reclassification or not, but there is more data, there is different kinds of testing procedures, there are different regulatory authorities that we can apply for control of risks.

Whether or not it is enough is what is going to be difficult by today's standards. But the reason we are where we are today is that technology has changed, knowledge base has changed, clinical information have changed, and that, at any point in time then, can be used to take a look at

what the most appropriate class is. And so, it isn't anything magical. It is just a matter of time and knowledge base in both the pre-clinical and the clinical arena that can really be the force behind reclassification.

DR. EDMONDSON: Now with regard to special controls, pre-market special controls, clinical research before marketing under Class II versus PMA how does that work.

MR. DILLARD: Well, let me give a general answer. Maybe I gave this earlier in one of the other sessions. We do have the ability as an agency, as FDA to ask for clinical data for Class II 510(k)able products.

The issue would be, and we tend to be an issue-based organization, that we try to look at the right amount of data to answer whatever the issues are associated with the product.

So, of you looked at it as a bottom-up kind of situation, many times we will look at it and we'll say there is a certain level of issues we have to answer and if pre-clinical information can answer those issues, then that would be enough to make a decision of substantial equivalence.

We wouldn't just inappropriately or

halfheartedly ask for an animal study, for instance or a clinical study.

We should be asking for data that answers an issue, and then we need the right kind of study to answer the issue. Pre-clinical or animal or clinical data may be appropriate under those circumstances. So, that option is available to us under 510(k) and may be necessary under circumstances where there's either product modifications or new products that are trying to get on the market.

From the standpoint of, and there's a lot I could say but I am going to try to say enough to give you a clearer picture about may be the difference between Class III and Class II and clinical data because that is a very sticky point and a very tough issue. If you are going to base purely on clinical data, when is clinical data for Class II any different than clinical data for Class III and where do you draw that line? And that isn't cast in stone. But one of the tests that I think has been used for classification and reclassification is, is that if the kind of clinical information that would be needed for a next of a kind device, would be clinical data that,

where there is a well-established knowledge base of clinically what happens in the safety and effectiveness arena, and what you were doing was getting clinical data to show that it was equivalent, that there wasn't any new issues, it wasn't necessarily or didn't necessarily need to be something that absolutely demonstrated safety and effectiveness, because that is the different standard for a PMA device versus equivalence for a 510(k) device, versus whether or not you really believe each individual device has to have its own clinical data set, that prospectively is defined so that you can a priori say it is a safe and effective device before it is on the market, that's kind of the Class III standard.

And so, if the clinical data, if you believe there has to be that level of clinical data then perhaps what you might be saying that it, that no, you still think it needs to be a Class III device, versus equivalent data, there is a good body of knowledge and you just need to show that you fit within a well-known and well-defined scheme of clinical performance, then that might be more towards a Class II kind of recommendation.

I hope that has helped and not confused.

CHAIRPERSON CANADY: Other questions or comments? We can begin with the form then, our favorite form. We will do this similarly to last time, in which the first three questions we will do as a straight vote. I think there will be some comments as we get further on and we will invite some conversation. The first one is, "Is this device life-threatening or life-supporting?"

Again the industry and consumer reps don't vote. I've learned something. All who would say yes, please raise your hands. No, please raise your hands. Six nos.

"Is the device for a use which is of substantial importance in preventing impairment of human health?"

Yes, please raise hands. No, please raise hands. I have three votes on one side. Gentlemen are you abstaining or -- ?

DR. GONZALES: I am actually still thinking about a yes vote. So that --

CHAIRPERSON CANADY: Okay. That's fine.

DR. GONZALES: You are asking for nos, right now correct?

CHAIRPERSON CANADY: We started with yeses. Is everybody ready to vote, let me start

with that? Are you ready?

DR. GONZALES: I am ready, now.

CHAIRPERSON CANADY: Okay. We'll start. Second question, "Is the device for a use which is of substantial importance in preventing impairment of human health?"

Yeses, please raise your hand.

Three yeses. Nos, please raise your hand.

Three nos. I am going to vote no as the tie-breaker.

Number three, "Does the device present a potential unreasonable risk of illness or injury?" Are we ready for a vote or more thought? I didn't write the questions. All who would say yes, please raise your hand. All who would say no, please raise your hand. Five.

UNIDENTIFIED: I abstain.

CHAIRPERSON CANADY: You abstain. Very good. Number four is obvious, that we said as a group, no, to all of the questions above. I note again, individually you complete your form as you see fit. It is important not to follow the group on your own personal form. That takes us to item number five, correct?

MS. SHULMAN: Correct.

CHAIRPERSON CANADY: "Is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness?"

All who would say yes. All who would say no. Six nos.

Number six, "Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness?"

All who would say yes. That is five.

All who would say no. Five yeses, one abstention.

DR. GATSONIS: The form is a little confusing. It says if you said yes to any of the first three then you have to go to item seven. So, you don't answer five or six.

MS. SHULMAN: Correct. But we didn't say yes to any of the first three.

DR. GATSONIS: But if somebody did.

CHAIRPERSON CANADY: Now, I think we get to number seven which is a delineation of what we think those special controls should be.

Let's do it similar to how we did last time; I will go by the grouping they have, and then

we'll open conversation for any additional ones.

Post market surveillance? All in favor? Five.

MS. SHULMAN: You didn't answer yes or no to that one.

CHAIRPERSON CANADY: We didn't have to. I am not going to put them on the spot again. Okay. All in favor of performance standards?

DR. KU: I have a question.

CHAIRPERSON CANADY: Yes?

DR. KU: With performance standards, can you specify rates of failure of the device?

MS. SHULMAN: You certainly can. Performance standards are the ones recognized by rule making.

DR. KU: Oh, you mean like the AMI standard for example.

By rule making through the FDA.

MS. SHULMAN: Relax your hand for a second.

DR. KU: So you can say that current failure rate is three percent, and we'd want to be sure that you guys meet three percent or better?

MS. SHULMAN: Maybe I'm wrong.

MR. DILLARD: No. No. I just want to

clarify.

This is a point that everybody gets stuck on every time we do this form. The performance standards are ones -- you've probably never seen one. One that we have been working on for 15 years and I believe went final was one on apnea monitors. And one that you may have seen was on cable and leads, male and female cables and leads. It was based on a number of reported deaths of plugging a male lead into a wall socket; being able to do that. That is an FDA-mandated performance standard that all manufacturers of the kind of product have to adhere to.

We have to go out with a proposed rule, get comments and then go final, just like we would in any rule-making like a classification process.

That is specifically what we are talking about here for performance standards.

So, any other kind of standard, an industry standard, either consensus or non-consensus, an international standard, that type of thing, you would want to put under "Other" in terms of standards. So, if you believe though we need to promulgate an FDA-based performance standard for these products, that is where you

would check yes on this one.

CHAIRPERSON CANADY: Any other questions for clarification?

DR. GONZALES: So, since the issue is the battery and battery function, and problems with the battery, the implantable, would that be under performance standards, to look at that subtype very specifically and in detail? Or would that be under "Other"?

MR. DILLARD: It could be either one. I know that is not the answer you are looking for, but the fact of the matter is that if you are concerned about a specific component of a device, but you believe there is already existing, and I'm not saying there is or isn't, but already existing industry standard, for example, that covers battery life, that has been referenced, that you believe is imperative for any manufacturer of kind of this product to meet that standard, but it is a consensus standard, an AMI standard or an ANSI standard, that would go under "Other".

If you think we need to take not only that knowledge but FDA knowledge and other general knowledge about batteries and actually promulgate a performance standard that would be a regulatory

standard, then you would check performance standard here.

DR. GONZALES: Then could I ask Dr. Walker to comment on whether there is a standard for battery failure? Not just failure in terms of loss of power, but failure in terms of other aspects of failure in terms of leakage, toxicity, other problems.

Are there such standards?

DR. WALKER: I am not aware of any voluntary trade or non-proprietary standards?

Medtronic may have a standard that they use internally, but that is not, I don't think that's what we are talking about here.

DR. GONZALES: So, then I believe that the battery function as far as abnormalities of the battery would be under "Other" since there is no standard performance.

CHAIRPERSON CANADY: So lets, are we ready to vote on the issue of performance standards now? All in favor, yes?

All opposed? One, two, three, four, five, six.

Patient registries? All in favor? All opposed?

All confused?

Is there confusion on this? There looks like there's confusion.

Can we clarify that category?

DR. WITTEN: I mean you want clarification on what, on what is a registry?

CHAIRPERSON CANADY: That's correct.

DR. WITTEN: It is a record of the patients who have received the product. But I don't think, it doesn't mean that we do actively get information about what has happened.

MR. DILLARD: Jim Dillard.

From the standpoint of a registry here, many manufacturers, and this is different than post-market surveillance because surveillance would actually be something that they would actively be doing, but a registry here would serve more as perhaps something that a manufacturer would try to get as much information as they could on a patient, by postcard, by record of what they're doing. To keep an ongoing log of the types of patients and some small amount of data that is going on.

But to be able to have some information but not necessarily to the extent that post-market surveillance is looking for perhaps something

specifically that may need to be clarified later on with data.

MS. WOJNER: Clarification.

So, in other words you can do post-market surveillance without a patient registry, but you can't do, but it doesn't work the other way. Because you need to have some form of a registry in place to do post-market surveillance. But the registry itself is not enough to give you the degree of data necessary to support?

MR. DILLARD: I almost think of it as a hierarchy and hopefully this doesn't bias anybody. But I think of a post-approval study, for example, as being the highest form of kind of post-approval requirements. You actually have to go do something that is prospective, post-market study to either gather some information or answer some question, and it would be intended to gather some data to support an issue that perhaps came up in the approvability of a device, for example.

Surveillance would be more on the end of perhaps looking for trends of something that might have been a low-level adverse event but you're really trying to answer it, but you're trying to get a broad data base to give you a sense of

whether or not it is different than your pre-market study, for example. But it would be something where you'd be looking for some data but not necessarily from a real prospective, post-approval type of study.

And then I would go one step further down, a patient registry would not be focused on data or a specific issue, but nonetheless, some information that the manufacturer could use in the future either to support a multitude of things that I've heard about. I mean from the standpoint of other kinds of claims, to try to further clarify some rates they may have put in their labeling when it was approved or reclassified, could be used for legal purposes too -- to have some data that would be broad based after the product was approved.

I think there is a multitude of reasons why and how you could use that.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: Can I ask one more clarifier in relation to that? Who decides which data are collected in that post-market surveillance category?

MR. DILLARD: If you recommended, and we, in a reclassification effort or an approval of

a product, either one, thought that post-market surveillance was necessary. You heard some I think, in training about what some of our authorities are in post-market surveillance, and there is no longer any required post-market surveillance based on FDA as of May, 1997.

It is all discretionary post-market surveillance. So, it would be a discussion between us and the manufacturer to come to an agreement on a post-market surveillance effort and what kind data, and OSB, FDA I guess, I should say, yes, and the manufacturer to come to an agreement on what at what would need to be in that study and what kind of data we were going to gather.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: So, the long and short of it is that we are recommending post-market surveillance, by default, there is a registry.

MR. DILLARD: I can't definitively say that. But I can say in general, that would be a higher order of the level of post-market activity that would be needed.

CHAIRPERSON CANADY: Other questions? Are we ready to vote on that issue? "Patient Registries."

All in favor yes? No?

Four positives

"Device tracking." All in favor --

DR. WALKER: Can I get a point of clarification?

CHAIRPERSON CANADY: Sure.

DR. WALKER: I thought we decided we were going to track which device goes into which patient.

CHAIRPERSON CANADY: We are; that was the default.

DR. WALKER: That is the patient registry?

CHAIRPERSON CANADY: That is going to be our recommendation, yes.

DR. WALKER: Then what is device tracking?

MS. SHULMAN: Just the device versus the patient. One, where is the device and where is the patient. Sometimes they aren't in the same place.

(Laughter.)

Not necessarily with this device, but for this form.

DR. WITTEN: Can I just clarify? As Mr. Dillard just said it is a hierarchy and device

tracking is just knowing where the device is, which usually is with the patient, but not actually gathering any information.

Just in case for example, there was a problem with the device and you needed to contact the patients because of some safety concern that had arisen.

CHAIRPERSON CANADY: Questions clarified?

Shall we vote on this issue, "device tracking"? Yes? No?

"Testing guidelines". Yes? Yeses for testing guidelines? Yes?

Clarification for "testing guidelines"?

MR. DILLARD: Jim Dillard.

There is not a huge distinction here between testing guidelines and guidance documents and other standards that you would recommend. I think if there were a known guideline, termed a guideline, or even a guidance document, we use guideline and guidance fairly interchangeably about what they mean as opposed to a standard which brings with it a little bit different connotation.

So here, if there is a known guideline that you know of, and it may not be an FDA-

promulgated guideline, but it might be a professional society guideline, it might be the Society of Professional Engineers; it might be the American Academy of Neurological Surgeons; it might have to do with some sort of testing and you know about it; you might check it and then reference what it is that testing guideline is. So it is a very nondescript way to attack the guideline guidance issue.

CHAIRPERSON CANADY: Other questions? All in favor of "testing guidelines"? All opposed? I have two and two; I am going to say No. That would be three and two. Other? Ms. Wojner?

MS. WOJNER: Yes. Could we, or could the panel specify under the "Other" category, specific post-market surveillance data that we would feel worth of collection in a CQI or whatever process we're going to call this?

CHAIRPERSON CANADY: I don't see why not. Yes. The floor is now open to such recommendations regarding anything additional people would like to see added to the special controls.

DR. GONZALES: Since we voted against performance standards because they don't exist

regarding battery function, and that was the crux of the potential problem or difference, a standard or some set of follow up for battery and battery function now it seems to me needs to be discussed and a direction given to the company. And I think that the person who is the expert is Dr. Walker, so I would really put it in his lap to help us with that kind of standard development, or direction.

DR. WALKER: Well, let me see what I can do. There exists a standard that says how these devices should be tested and what sort of load they should be tested on and what are the minimum and maximum rates. Perhaps we might, by reference, want to incorporate that standard for output and biphasic and no DC and that sort of thing. I think that is a good standard because I was on the committee that wrote it, along with Dr. North.

With respect to battery output, certainly one option that we have would be to impose on this indication for a Class II device the same sorts of annual reports, biannual inspection and pre-market visits that are imposed on a Class III implantable device.

My recommendation would be to adopt what is already being done with other Class III

implantable stimulators, rather than trying dream up our own as we sit here on a Friday afternoon.

CHAIRPERSON CANADY: So are we saying then that the standard that we want is the same post-market standard as a Class III but not the same pre-market standard?

DR. WALKER: Correct, because the Class III requires clinical trials.

CHAIRPERSON CANADY: Is that a reasonable thing from the FDA's perspective?

MS. MAHER: Well, this is Sally, can I say something? The annual report aspect is actually a requirement of the PMA procedure and how you handle the PMA section of the law. It is not part of the 510(k) substantially equivalent section.

So, I think what you are actually asking for needs to defined more clearly here, such as some sort of annual report on the performance on the device, not an annual report as defined under the PMA sections. I am not quite sure what you are looking for, but I don't think you are looking at a PMA annual report type of thing.

CHAIRPERSON CANADY: I'm looking for an annual report on battery-related complications.

DR. WALKER: Sure. Device failures.

DR. EDMONDSON: I think, too, before a special control pre-market special control too should include a limited clinical study to look at the hardware performance of the IPG itself with regard to any inopportune stimulation, battery function in situ. Just those two things, I think.

CHAIRPERSON CANADY: Dr. Ku?

DR. KU: I am not convinced that a clinical study is needed. I mean, if you can bench-top test this thing and achieved a reliability of .03 percent failure rate for 100 different devices, then implanting it, the technology is known.

CHAIRPERSON CANADY: Well, let's put the two recommendations for "Other" to a vote. And I think that will resolve.

One would be "that there would be an annual report regarding device failures". All in favor? That is six. Opposed? There's nobody left.

"That there would be a clinical study regarding hardware performance." All in favor?

All in favor?

DR. EDMONDSON: Can I make a comment?

CHAIRPERSON CANADY: Sure.

DR. EDMONDSON: Again, before the motion.

CHAIRPERSON CANADY: Only if you don't like the vote.

DR. EDMONDSON: I would like to make another push for a clinical study before release. There are many nuances that really you can test in the laboratory to determine frequency, output, all of these engineering issues. But when you implant the device and somebody goes out and they mow their lawn and a number of other things, there may be some nuances intrinsic to that device. So I think that a limited study with focused questions is really warranted.

CHAIRPERSON CANADY: Okay we will put that question to a vote a second time. All in favor raise your hand. Dr. Edmondson, you're in favor, raise your hand. All opposed. Three, four to two, opposed.

MS. WOJNER: Dr. Canady, I just want to let the record state that I think that Dr. Gonzales has brought up some very important points about a 25 percent "Other" section and I would hope that FDA and the manufacturing sector would do something

logically about coming up with some very clear descriptors other than a broad-based "Other" section so that we are absolutely certain of what is occurring.

CHAIRPERSON CANADY: Other comments.

Dr. Gonzales?

DR. GONZALES: I have changed my vote because now that we have included reports on performance, complications, failures and inspections up to Class III standards, I am satisfied that now the downgrading of the change of the classification from III to II, now that I know we are able to impose those kinds of follow ups, restrictions, and inspections, and up to this point I was not aware that we would be able to do that.

CHAIRPERSON CANADY: I'm not sure we have done that.

DR. GONZALES: Well, but we may do that.

CHAIRPERSON CANADY: We have recommended, and I'll just remind everybody that we are recommending that there be an annual report of device failures. That is the only additional standard other than the ones that we have voted on that we've added. If there are additional things that we wish to add, such as inspections, then we

need to say that. Dr. Walker?

DR. WALKER: I had put up a foil with some suggested changes to the labeling. Would this be an appropriate time to add those to our laundry list?

CHAIRPERSON CANADY: It would be. Does everyone recall them or do we need to see them again? The issues of language. Can we vote that we recommend those changes? All in favor raise your hand. All opposed? I believe that completes number seven.

DR. GONZALES: Can I make a recommendation that, as Dr. Walker stated earlier, that inspections to the Class III standards be imposed?

CHAIRPERSON CANADY: Yes. And I would ask that we vote on that. All in favor of that? Opposed? That is yes, six.

MS. MAHER: Before we move on, could I ask Jim Dillard how that would be moved forward, in interaction with the compliance and evaluation group?

MR. DILLARD: Jim Dillard. In terms of that recommendation up to Class III standards of inspection, I think I can tell you how we would

interpret that recommendation which is what I think Sally is getting at.

The interpretation of that in my mind would be that we put this in the higher kickup category to do what we should be doing by regulation, which is, inspect every couple of years, do a full inspection. Certainly, in this particular product line for a manufacturer because the fact of the matter is when we go in and do an inspection at a manufacturing facility and the manufacturer may have multiple lines of products, we don't go inspect every line and every procedure. We obviously go in and take some statistical samplings and look at various aspects of a process and see whether or not, in general, they are in compliance with the quality system regulation.

I think the interpretation that I would take away from this is that you are saying is what we should do is we should inspect every two years not every five years because it is one of those devices that should have a kick-up factor. Number two, it ought to be a target of every inspection that we go into that facility, is to make sure that we inspect this particular product and product line every time, in addition to others that we might

look into also.

But from the standpoint of a pre-clearance inspection which a Class III PMA product would have, that generally would not be something that we would do nor would we probably make that a high priority; to make sure that every time a manufacturer had this kind of product, if it was under 510(k) to inspect them pre-approval for compliance with quality system regulations. That is probably not something that will come out of this. But I think that by bringing these issues up, I mean, the fact of the matter is, and maybe I can clarify one thing: number one is, yes, you are making a recommendation. I agree with Dr. Canady on that. The other thing is just your mere discussion on this and having a strong position helps us then to focus on those issues when we are making our final regulatory action.

So, keep that in mind too, when you're discussing the particular issues.

DR. KU: Can we make pre-market inspection part of this recommendation? The reason is that I think we are breaking new ground and I think that may be something that may be warranted. This obviously can be re-reviewed for

reclassification again in five years, or whatever.

MR. DILLARD: Dr. Canady, would you like me to comment on that again?

CHAIRPERSON CANADY: I guess I want to comment on that. I guess I am not sure that accomplishes what we want, as I think about it. The real issue is whether there is going to be battery failure. I am not sure that can be addressed directly at the pre-market inspection.

DR. KU: But don't they need to evaluate the entire manufacturing process at that time? Or is that already done?

CHAIRPERSON CANADY: I think that would be part of the normal process, in terms of the discussion.

Mr. Dillard?

MR. DILLARD: The inspection, without going into great detail about what we do on inspection, whether it is a Class III or a Class II, if we are inspecting the product line we'll go in and look at the processes that the manufacturer has, we'll look at the specifications, we'll look to see whether they have tested in accordance with the specifications and have written down and logged the kind of data that goes into it, that to me in

my mind isn't too different between a Class III and a Class II device.

You look for the same veracity in the data, and their adherence to their own internal processes, that they have to do the specific things that you are talking about and focussing on, in terms of battery testing, overall product testing, hermetic sealing in this case and everything else.

We would assume there would be a process in place to look at that and that the manufacturers tested in accordance with their specifications. And we would look for that.

CHAIRPERSON CANADY: Ms. Wojner?

MS. WOJNER: I was just going to say that I guess my advice to the Committee would be that if we are going to add much more to the list then are we really making the right decision to say that this is a Class II because I am not sure that we need to go so far as a pre-market inspection.

I think the task before us at hand is to ensure that if we are going to go to Class II that we are ensuring a certain degree of quality, standardization and I think that what is on the list right now accomplishes that.

CHAIRPERSON CANADY: Other comments?

Can we then vote on that issue of whether we wish to include a pre-market inspection.

DR. KU: I'll withdraw that.

CHAIRPERSON CANADY: You withdraw it? Fine. Then I would like to go over question seven as it now is constituted which would be to have post-market surveillance, patient registries, device tracking, inspection at Level III and device failure reporting on an annual basis. And I would ask for a yes vote on that.

Yes is do you agree to the package? You've done it piece by piece.

All nos. That's a five one.

UNIDENTIFIED SPEAKER: No, no, it's a six.

CHAIRPERSON CANADY: You're correct.

DR. WITTEN: Can I ask for some clarification on two things? One is that you haven't commented here anywhere on those things that the sponsor suggested as special controls. Were you meaning to include some or none or all of those, the standards that they suggested, the other things that were in the petition, I mean the sponsor of the reclassification petition. That was one question. And the other thing is that I wasn't

sure what you were voting on. The list, or the yes or no, is there sufficient information to establish special controls.

CHAIRPERSON CANADY: We were voting on the overall package, which would be including what components constituted special controls.

MS. SHULMAN: Okay, then I guess it is just a matter of housekeeping to make sure that nobody is confused. If you just want to vote first, I know it is a repeat of question six, but just yes or no to classify it into Class II. It's the first part of question seven, is there sufficient information to establish special controls. I know that's what you all have been speaking about. But if you just can get a vote for the record.

CHAIRPERSON CANADY: All in favor of special controls? Yes. No. Five - one.

MS. SHULMAN: Okay.

CHAIRPERSON CANADY: Now, the special control. Do we want to address the special controls as presented by ANS? Which addressed a number of exacting standards, actually.

Dr. Walker?

DR. WALKER: Let me suggest that we

adopt them. I have suggested some changes to them and let's adopt them.

CHAIRPERSON CANADY: All in favor of that approach say aye. Raise your hand. Six - nil.

Okay. I believe that may complete question seven to everyone's satisfaction. Okay.

Number eight; is a regulatory performance standard needed, required to provide reasonable assurance of the safety and effectiveness of a Class II or III device.

MS. SHULMAN: You can skip question eight and we can skip nine because that goes with question eight. We can skip question ten because that is for PMAs.

CHAIRPERSON CANADY: Okay. We are back to number 11, "Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use because of any potentiality for harmful effects or the collateral measures necessary for the device's use.

MS. SHULMAN: Please remember voting no makes it a prescription device.

CHAIRPERSON CANADY: All in favor raise

your hand. All opposed. Six nos.

The first one is "Only upon the oral or written authorization of a practitioner, licensed by law to administer or use the device." All yeses raise your hand. Nos?

The next one would be, "Use only by persons with specific training or experience in its use."

Yes?

MS. WOJNER: Point of clarification on that.

Does that second category encompass technicians that are involved in programming these devices once they have been implanted?

CHAIRPERSON CANADY: That you would have to make as a recommendation.

She is presuming that the programming may not be done by physicians.

MS. SHULMAN: Usually it is not.

CHAIRPERSON CANADY: That is what I am saying. So should there be special training?

MS. WOJNER: Are you waiting for an answer?

CHAIRPERSON CANADY: I guess my view is that it would be done under the direction of a

physician and that the training should be so specified in that context.

MS. WOJNER: Okay. Would that include a licensed nurse practitioner or a clinical nurse specialist, for instance? Or would they fall in the first category?

CHAIRPERSON CANADY: I would not give them independent, no. But that is my personal view. The panel might have a different view.

Are you ready to vote on this issue? "Use only by persons with specific training or experience in its use." Yes? Three yeses. No? Three nos. I am going to say no, as a tie-breaker.

"Use only in certain facilities." Yeses? Raise your hands. Nos? Six. Any other restrictions that the panel would feel need to be applied or would like to apply? I believe we have completed this form.

MS. SHULMAN: All right, now we have the second one.

CHAIRPERSON CANADY: Do we have to vote on the form?

MS. SHULMAN: You may vote on both of them together.

CHAIRPERSON CANADY: Okay, good. Under

question four, indications for use, I would suggest that we are not proposing any changes in the indications, are we?

MS. SHULMAN: So, we can put on there, as in the reclassification petition?

CHAIRPERSON CANADY: Right. "Identification of any risks to health presented by device." Comments? As in the reclassification position. Recommended advisory panel classification, Class II.

Do we still need to put a priority on this one, Dr. Witten?

DR. WITTEN: Yes, they still need to put high, medium or low.

CHAIRPERSON CANADY: High, medium or low priority.

DR. WITTEN: Right.

CHAIRPERSON CANADY: Any comments?

All in favor of high, raise your hand.

Medium?

Low?

"If the device is an implant or is life-sustaining or life-supporting, and has been classified in a category other than Class III, explain fully the reasons for the lower

classification with supporting documentation and data.

The summary of information would be the presentations made here today, the petition and the written material distributed. Any additional information people would like to include under the last category?

Any additional restrictions people would like to place?

Any comments or questions before we vote on the two documents?

MS. SHULMAN: There is one more question.

On the back of that you can skip question ten because that is for Class I device. And it's just question eleven, "existing standards to the device, device or some assembly components or device materials, parts and accessories."

CHAIRPERSON CANADY: Any comments or questions?

Hearing none, we will vote now on accepting the documents together as completed by the group.

All in favor, raise your hand.

All opposed?

So five-one.

Other business?

The next meeting of this panel will be December 10, 1999.

Otherwise, we will now adjourn.

DR. WITTEN: I'd like to thank the panel and the FDA and the industry people who have been here today for your help.

(Whereupon, the proceedings went off the record at 3:29 p.m.)